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<p>(21) International Application Number: PCT/US99/17132</p> <p>(22) International Filing Date: 28 July 1999 (28.07.99)</p> <p>(30) Priority Data:</p> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 30%;">09/123,494</td> <td style="width: 40%;">28 July 1998 (28.07.98)</td> <td style="width: 30%;">US</td> </tr> <tr> <td>Not furnished</td> <td>28 July 1998 (28.07.98)</td> <td>US</td> </tr> <tr> <td>09/152,814</td> <td>14 September 1998 (14.09.98)</td> <td>US</td> </tr> <tr> <td>Not furnished</td> <td>14 September 1998 (14.09.98)</td> <td>US</td> </tr> <tr> <td>09/173,482</td> <td>14 October 1998 (14.10.98)</td> <td>US</td> </tr> <tr> <td>Not furnished</td> <td>14 October 1998 (14.10.98)</td> <td>US</td> </tr> <tr> <td>60/106,889</td> <td>3 November 1998 (03.11.98)</td> <td>US</td> </tr> <tr> <td>60/109,093</td> <td>19 November 1998 (19.11.98)</td> <td>US</td> </tr> <tr> <td>60/113,796</td> <td>22 December 1998 (22.12.98)</td> <td>US</td> </tr> <tr> <td>09/229,005</td> <td>12 January 1999 (12.01.99)</td> <td>US</td> </tr> <tr> <td>Not furnished</td> <td>12 January 1999 (12.01.99)</td> <td>US</td> </tr> </table> <p>(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Applications</p> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 30%;">US</td> <td style="width: 40%;">Not furnished (CIP)</td> <td style="width: 30%;"></td> </tr> <tr> <td>Filed on</td> <td>28 July 1998 (28.07.98)</td> <td></td> </tr> <tr> <td>US</td> <td>09/123,494 (CIP)</td> <td></td> </tr> <tr> <td>Filed on</td> <td>28 July 1998 (28.07.98)</td> <td></td> </tr> <tr> <td>US</td> <td>09/152,814 (CIP)</td> <td></td> </tr> <tr> <td>Filed on</td> <td>14 September 1998 (14.09.98)</td> <td></td> </tr> <tr> <td>US</td> <td>Not furnished (CIP)</td> <td></td> </tr> <tr> <td>Filed on</td> <td>14 September 1998 (14.09.98)</td> <td></td> </tr> <tr> <td>US</td> <td>09/173,482 (CIP)</td> <td></td> </tr> <tr> <td>Filed on</td> <td>14 October 1998 (14.10.98)</td> <td></td> </tr> <tr> <td>US</td> <td>Not furnished (CIP)</td> <td></td> </tr> <tr> <td>Filed on</td> <td>14 October 1998 (14.10.98)</td> <td></td> </tr> <tr> <td>US</td> <td>60/106,889 (CIP)</td> <td></td> </tr> <tr> <td>Filed on</td> <td>3 November 1998 (03.11.98)</td> <td></td> </tr> <tr> <td>US</td> <td>60/109,093 (CIP)</td> <td></td> </tr> <tr> <td>Filed on</td> <td>19 November 1998 (19.11.98)</td> <td></td> </tr> <tr> <td>US</td> <td>60/113,796 (CIP)</td> <td></td> </tr> <tr> <td>Filed on</td> <td>22 December 1998 (22.12.98)</td> <td></td> </tr> <tr> <td>US</td> <td>09/229,005 (CIP)</td> <td></td> </tr> <tr> <td>Filed on</td> <td>12 January 1999 (12.01.99)</td> <td></td> </tr> <tr> <td>US</td> <td>Not furnished (CIP)</td> <td></td> </tr> <tr> <td>Filed on</td> <td>12 January 1999 (12.01.99)</td> <td></td> </tr> </table> <p>(71) Applicant (for all designated States except US): INCYTE PHARMACEUTICALS, INC. [US/US]; 3174 Porter Drive, Palo Alto, CA 94304 (US).</p>			09/123,494	28 July 1998 (28.07.98)	US	Not furnished	28 July 1998 (28.07.98)	US	09/152,814	14 September 1998 (14.09.98)	US	Not furnished	14 September 1998 (14.09.98)	US	09/173,482	14 October 1998 (14.10.98)	US	Not furnished	14 October 1998 (14.10.98)	US	60/106,889	3 November 1998 (03.11.98)	US	60/109,093	19 November 1998 (19.11.98)	US	60/113,796	22 December 1998 (22.12.98)	US	09/229,005	12 January 1999 (12.01.99)	US	Not furnished	12 January 1999 (12.01.99)	US	US	Not furnished (CIP)		Filed on	28 July 1998 (28.07.98)		US	09/123,494 (CIP)		Filed on	28 July 1998 (28.07.98)		US	09/152,814 (CIP)		Filed on	14 September 1998 (14.09.98)		US	Not furnished (CIP)		Filed on	14 September 1998 (14.09.98)		US	09/173,482 (CIP)		Filed on	14 October 1998 (14.10.98)		US	Not furnished (CIP)		Filed on	14 October 1998 (14.10.98)		US	60/106,889 (CIP)		Filed on	3 November 1998 (03.11.98)		US	60/109,093 (CIP)		Filed on	19 November 1998 (19.11.98)		US	60/113,796 (CIP)		Filed on	22 December 1998 (22.12.98)		US	09/229,005 (CIP)		Filed on	12 January 1999 (12.01.99)		US	Not furnished (CIP)		Filed on	12 January 1999 (12.01.99)		<p>(72) Inventors; and (75) Inventors/Applicants (for US only): HILLMAN, Jennifer, L. 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<p>(54) Title: PHOSPHORYLATION EFFECTORS</p> <p>(57) Abstract</p> <p>The invention provides human phosphorylation effectors (PHSP) and polynucleotides which identify and encode PHSP. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating, or preventing disorders associated with expression of PHSP.</p>																																																																																																							

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PHOSPHORYLATION EFFECTORS

TECHNICAL FIELD

5 This invention relates to nucleic acid and amino acid sequences of phosphorylation effectors and to the use of these sequences in the diagnosis, treatment, and prevention of cell proliferative, immune, and neuronal disorders.

 Kinases and phosphatases are critical components of intracellular signal transduction mechanisms. Kinases catalyze the transfer of high energy phosphate groups from adenosine triphosphate (ATP) to various target proteins. Phosphatases, in contrast, remove phosphate groups from proteins. Reversible protein phosphorylation is the main strategy for regulating protein activity in eukaryotic cells. In general, proteins are activated by phosphorylation in response to extracellular signals such as hormones, neurotransmitters, and growth and differentiation factors.

10 Protein dephosphorylation occurs when down-regulation of a signaling pathway is required. The coordinate activities of kinases and phosphatases regulate key cellular processes such as proliferation, differentiation, and cell cycle progression. Kinases comprise the largest known enzyme superfamily and are widely varied in their substrate specificities. Kinases may be categorized based on the specific amino acid residues that are phosphorylated in their substrates:

15 protein tyrosine kinases (PTK) phosphorylate tyrosine residues, and protein serine/threonine kinases (STK) phosphorylate serine and/or threonine residues. Almost all kinases contain a conserved 250-300 amino acid catalytic domain. This domain can be further divided into 11 subdomains. N-terminal subdomains I-IV fold into a two-lobed structure which binds and orients the ATP donor molecule, and subdomain V spans the two lobes. C-terminal subdomains VIA-XI

20 bind the protein substrate and transfer the gamma phosphate from ATP to the hydroxyl group of a serine, threonine, or tyrosine residue. Each of the 11 subdomains contains specific catalytic residues or amino acid motifs characteristic of that subdomain. For example, subdomain I contains an 8-amino acid glycine-rich ATP binding consensus motif, subdomain II contains a critical lysine residue required for maximal catalytic activity, and subdomains VI and IX comprise

25 the highly conserved catalytic core. Kinases may also be categorized by additional amino acid sequences, generally between 5 and 100 residues, which either flank or occur within the kinase domain. These additional amino acid sequences regulate kinase activity and determine substrate specificity. (Reviewed in Hardie, G. and Hanks, S. (1995) The Protein Kinase Facts Books, Vol I:7-20 Academic Press, San Diego, CA.)

35 STKs include both protein kinase A (PKA) and calcium-dependent protein kinase C

(PKC), both of which transduce signals from plasma membrane receptors. The activities of PKA and PKC are directly regulated by second messenger signaling molecules such as cyclic AMP and diacylglycerol, respectively. A novel kinase identified by genetic analysis in the fission yeast Schizosaccharomyces pombe is encoded by the *cek1*⁺ gene and is related to both PKA and PKC

5 (Samejima, I. and Yanagida, M. (1994) Mol. Cell. Biol. 14:6361-6371). *cek1*⁺ encodes an unusually large kinase of 1309 amino acids. The kinase domain spans residues 585 to 987, and 112 additional amino acids are present in this domain between subdomains VII and VIII. Overexpression of *cek1*⁺ suppresses mutations in *cut8*⁺, a gene required for chromosome segregation during mitosis. Therefore, *cek1*⁺ may encode a unique member of the PKA/PKC

10 protein family with a role in mitotic signaling and cell cycle progression.

PTKs may be classified as either transmembrane or nontransmembrane proteins. Transmembrane tyrosine kinases function as receptors for most growth factors. Binding of growth factor to the receptor activates the transfer of a phosphate group from ATP to selected tyrosine side chains of the receptor itself and other specific second messenger proteins. Growth factors

15 (GF) that associate with receptor PTKs include epidermal GF, platelet-derived GF, fibroblast GF, hepatocyte GF, insulin and insulin-like GFs, nerve GF, vascular endothelial GF, and macrophage colony stimulating factor. Nontransmembrane PTKs form signaling complexes with the cytosolic domains of plasma membrane receptors. Receptors that signal through nontransmembrane PTKs include cytokine, hormone, and antigen-specific lymphocytic receptors. Many PTKs were first

20 identified as oncogene products in cancer cells in which PTK activation was no longer subject to normal cellular controls. In fact, about one third of the known oncogenes encode PTKs. Furthermore, cellular transformation (oncogenesis) is often accompanied by increased tyrosine phosphorylation activity (Charbonneau, H. and Tonks, N. K. (1992) Annu. Rev. Cell Biol. 8:463-93). Regulation of PTK activity may therefore be an important strategy in controlling some

25 types of cancer.

Some kinases utilize carbohydrates as their substrates and are important for glucose metabolism. For example, glycolysis employs four distinct kinases to effect the conversion of glucose to pyruvate, a key metabolite in the production of ATP. One of these enzymes is phosphofructokinase (PFK) which catalyzes the transfer of phosphate from ATP to fructose 6-

30 phosphate. PFK is an allosteric enzyme and a key regulator of glycolysis. In certain genetic muscle disorders, such as muscle phosphofructokinase deficiency type VII, phosphofructokinase activity is absent in muscle and deficient in red blood cells. As a result, afflicted individuals suffer from mild hemolytic anemia and muscle pain (Isselbacher, K.J. et al. (1994) Harrison's Principles of Internal Medicine, McGraw-Hill, New York, NY, p. 2102).

35 Kinase-mediated phosphorylation is antagonized by the activity of phosphatases, which

- remove phosphate groups by hydrolysis. Phosphatases are classified into one of three evolutionarily distinct families: the protein serine/threonine phosphatases (PPs), the protein tyrosine phosphatases, and the acid/alkaline phosphatases. PPs may be further categorized into four distinct groups: PP-I, PP-IIA, PP-IIB, and PP-IIC. (Cohen, P. (1989) *Annu. Rev. Biochem.* 58:453-508). PP-I, in particular, dephosphorylates many of the proteins phosphorylated by PKA and is therefore an important regulator of signal transduction pathways. Kinase-activated proteins which bind to and inhibit PP-I have been identified. These inhibitors potentiate the activity of kinases such as PKA by allowing protein substrates to remain in their phosphorylated, activated state. A novel inhibitor of PP-I has been purified from porcine aorta (Eto, M. et al. (1995) *J. Biochem.* 118:1104-1107; Eto, M. et al. (1997) *FEBS Lett.* 410:356-360). This inhibitor, called CPI17, is 147 amino acids in length and is activated by PKC. CPI17 expression is restricted to smooth muscle tissues such as aorta and bladder, suggesting that CPI17 functions in PKC-mediated signal transduction pathways in these tissues, possibly through a calcium-dependent mechanism.
- 15 The discovery of new phosphorylation effectors and the polynucleotides encoding them satisfies a need in the art by providing new compositions which are useful in the diagnosis, prevention, and treatment of cell proliferative, immune, and neuronal disorders.

SUMMARY OF THE INVENTION

20

The invention features substantially purified polypeptides, phosphorylation effectors, referred to collectively as "PHSP" and individually as "PHSP-1 to PHSP-31". In one aspect, the invention provides a substantially purified polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-31, and fragments thereof.

- 25 The invention further provides a substantially purified variant having at least 90% amino acid identity to at least one of the amino acid sequences selected from the group consisting of SEQ ID NO:1-31, and fragments thereof. The invention also provides an isolated and purified polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-31, and fragments thereof. The invention also includes an
- 30 isolated and purified polynucleotide variant having at least 80% polynucleotide sequence identity to the polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-31, and fragments thereof.

- Additionally, the invention provides an isolated and purified polynucleotide which hybridizes under stringent conditions to the polynucleotide encoding the polypeptide comprising
- 35 an amino acid sequence selected from the group consisting of SEQ ID NO:1-31, and fragments

thereof. The invention also provides an isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide encoding the polypeptide comprising the amino acid sequence selected from the group consisting of SEQ ID NO:1-31, and fragments thereof.

The invention also provides a method for detecting a polynucleotide in a sample
5 containing nucleic acids, the method comprising the steps of (a) hybridizing the complement of the polynucleotide sequence to at least one of the polynucleotides of the sample, thereby forming a hybridization complex; and (b) detecting the hybridization complex, wherein the presence of the hybridization complex correlates with the presence of a polynucleotide in the sample. In one aspect, the method further comprises amplifying the polynucleotide prior to hybridization.

10 The invention also provides an isolated and purified polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:32-62, and fragments thereof. The invention further provides an isolated and purified polynucleotide variant having at least 80% polynucleotide sequence identity to the polynucleotide sequence selected from the group consisting of SEQ ID NO:32-62, and fragments thereof. The invention also provides an
15 isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:32-62, and fragments thereof.

The invention further provides an expression vector containing at least a fragment of the polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the
20 group consisting of SEQ ID NO:1-31, and fragments thereof. In another aspect, the expression vector is contained within a host cell.

The invention also provides a method for producing a polypeptide, the method comprising the steps of: (a) culturing the host cell containing an expression vector containing at least a fragment of a polynucleotide under conditions suitable for the expression of the polypeptide; and
25 (b) recovering the polypeptide from the host cell culture.

The invention also provides a pharmaceutical composition comprising a substantially purified polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NO:1-31, and fragments thereof, in conjunction with a suitable pharmaceutical carrier.

The invention further includes a purified antibody which binds to a polypeptide selected
30 from the group consisting of SEQ ID NO:1-31, and fragments thereof. The invention also provides a purified agonist and a purified antagonist to the polypeptide.

The invention also provides a method for treating or preventing a disorder associated with decreased expression or activity of PHSP, the method comprising administering to a subject in need of such treatment an effective amount of a pharmaceutical composition comprising a
35 substantially purified polypeptide having the amino acid sequence selected from the group

consisting of SEQ ID NO:1-31, and fragments thereof, in conjunction with a suitable pharmaceutical carrier.

The invention also provides a method for treating or preventing a disorder associated with increased expression or activity of PHSP, the method comprising administering to a subject in
5 need of such treatment an effective amount of an antagonist of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-31, and fragments thereof.

BRIEF DESCRIPTION OF THE TABLES

Table 1 shows nucleotide and polypeptide sequence identification numbers (SEQ ID NO),
10 clone identification numbers (clone ID), cDNA libraries, and cDNA fragments used to assemble full-length sequences encoding PHSP.

Table 2 shows features of each polypeptide sequence, including potential motifs, homologous sequences, and methods and algorithms used for identification of PHSP.

Table 3 shows the tissue-specific expression patterns of each nucleic acid sequence as
15 determined by northern analysis, diseases, disorders, or conditions associated with these tissues, and the vector into which each cDNA was cloned.

Table 4 describes the tissues used to construct the cDNA libraries from which cDNA clones encoding PHSP were isolated.

Table 5 shows the tools, programs, and algorithms used to analyze PHSP, along with
20 applicable descriptions, references, and threshold parameters.

DESCRIPTION OF THE INVENTION

Before the present proteins, nucleotide sequences, and methods are described, it is understood that this invention is not limited to the particular machines, materials and methods
25 described, as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise. Thus, for
30 example, a reference to "a host cell" includes a plurality of such host cells, and a reference to "an antibody" is a reference to one or more antibodies and equivalents thereof known to those skilled in the art, and so forth.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention
35 belongs. Although any machines, materials, and methods similar or equivalent to those described

herein can be used to practice or test the present invention, the preferred machines, materials and methods are now described. All publications mentioned herein are cited for the purpose of describing and disclosing the cell lines, protocols, reagents and vectors which are reported in the publications and which might be used in connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

DEFINITIONS

"PHSP" refers to the amino acid sequences of substantially purified PHSP obtained from any species, particularly a mammalian species, including bovine, ovine, porcine, murine, equine, and preferably the human species, from any source, whether natural, synthetic, semi-synthetic, or recombinant.

The term "agonist" refers to a molecule which, when bound to PHSP, increases or prolongs the duration of the effect of PHSP. Agonists may include proteins, nucleic acids, carbohydrates, or any other molecules which bind to and modulate the effect of PHSP.

An "allelic variant" is an alternative form of the gene encoding PHSP. Allelic variants may result from at least one mutation in the nucleic acid sequence and may result in altered mRNAs or in polypeptides whose structure or function may or may not be altered. Any given natural or recombinant gene may have none, one, or many allelic forms. Common mutational changes which give rise to allelic variants are generally ascribed to natural deletions, additions, or substitutions of nucleotides. Each of these types of changes may occur alone, or in combination with the others, one or more times in a given sequence.

"Altered" nucleic acid sequences encoding PHSP include those sequences with deletions, insertions, or substitutions of different nucleotides, resulting in a polynucleotide the same as PHSP or a polypeptide with at least one functional characteristic of PHSP. Included within this definition are polymorphisms which may or may not be readily detectable using a particular oligonucleotide probe of the polynucleotide encoding PHSP, and improper or unexpected hybridization to allelic variants, with a locus other than the normal chromosomal locus for the polynucleotide sequence encoding PHSP. The encoded protein may also be "altered," and may contain deletions, insertions, or substitutions of amino acid residues which produce a silent change and result in a functionally equivalent PHSP. Deliberate amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues, as long as the biological or immunological activity of PHSP is retained. For example, negatively charged amino acids may include aspartic acid and glutamic acid, positively charged amino acids may include lysine and arginine, and amino acids with uncharged polar head groups having similar hydrophilicity values may include leucine, isoleucine,

and valine; glycine and alanine; asparagine and glutamine; serine and threonine; and phenylalanine and tyrosine.

The terms "amino acid" or "amino acid sequence" refer to an oligopeptide, peptide, polypeptide, or protein sequence, or a fragment of any of these, and to naturally occurring or synthetic molecules. In this context, "fragments," "immunogenic fragments," or "antigenic fragments" refer to fragments of PHSP which are preferably at least 5 to about 15 amino acids in length, most preferably at least 14 amino acids, and which retain some biological activity or immunological activity of PHSP. Where "amino acid sequence" is recited to refer to an amino acid sequence of a naturally occurring protein molecule, "amino acid sequence" and like terms are not meant to limit the amino acid sequence to the complete native amino acid sequence associated with the recited protein molecule.

"Amplification" relates to the production of additional copies of a nucleic acid sequence. Amplification is generally carried out using polymerase chain reaction (PCR) technologies well known in the art.

The term "antagonist" refers to a molecule which, when bound to PHSP, decreases the amount or the duration of the effect of the biological or immunological activity of PHSP. Antagonists may include proteins, nucleic acids, carbohydrates, antibodies, or any other molecules which decrease the effect of PHSP.

The term "antibody" refers to intact molecules as well as to fragments thereof, such as Fab, F(ab')₂, and Fv fragments, which are capable of binding the epitopic determinant. Antibodies that bind PHSP polypeptides can be prepared using intact polypeptides or using fragments containing small peptides of interest as the immunizing antigen. The polypeptide or oligopeptide used to immunize an animal (e.g., a mouse, a rat, or a rabbit) can be derived from the translation of RNA, or synthesized chemically, and can be conjugated to a carrier protein if desired. Commonly used carriers that are chemically coupled to peptides include bovine serum albumin, thyroglobulin, and keyhole limpet hemocyanin (KLH). The coupled peptide is then used to immunize the animal.

The term "antigenic determinant" refers to that fragment of a molecule (i.e., an epitope) that makes contact with a particular antibody. When a protein or a fragment of a protein is used to immunize a host animal, numerous regions of the protein may induce the production of antibodies which bind specifically to antigenic determinants (given regions or three-dimensional structures on the protein). An antigenic determinant may compete with the intact antigen (i.e., the immunogen used to elicit the immune response) for binding to an antibody.

The term "antisense" refers to any composition containing a nucleic acid sequence which is complementary to the "sense" strand of a specific nucleic acid sequence. Antisense molecules may be produced by any method including synthesis or transcription. Once introduced into a cell,

the complementary nucleotides combine with natural sequences produced by the cell to form duplexes and to block either transcription or translation. The designation "negative" can refer to the antisense strand, and the designation "positive" can refer to the sense strand.

The term "biologically active," refers to a protein having structural, regulatory, or biochemical functions of a naturally occurring molecule. Likewise, "immunologically active" refers to the capability of the natural, recombinant, or synthetic PHSP, or of any oligopeptide thereof, to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies.

The terms "complementary" or "complementarity" refer to the natural binding of polynucleotides by base pairing. For example, the sequence "5' A-G-T 3'" bonds to the complementary sequence "3' T-C-A 5'." Complementarity between two single-stranded molecules may be "partial," such that only some of the nucleic acids bind, or it may be "complete," such that total complementarity exists between the single stranded molecules. The degree of complementarity between nucleic acid strands has significant effects on the efficiency and strength of the hybridization between the nucleic acid strands. This is of particular importance in amplification reactions, which depend upon binding between nucleic acids strands, and in the design and use of peptide nucleic acid (PNA) molecules.

A "composition comprising a given polynucleotide sequence" or a "composition comprising a given amino acid sequence" refer broadly to any composition containing the given polynucleotide or amino acid sequence. The composition may comprise a dry formulation or an aqueous solution. Compositions comprising polynucleotide sequences encoding PHSP or fragments of PHSP may be employed as hybridization probes. The probes may be stored in freeze-dried form and may be associated with a stabilizing agent such as a carbohydrate. In hybridizations, the probe may be deployed in an aqueous solution containing salts (e.g., NaCl), detergents (e.g., sodium dodecyl sulfate; SDS), and other components (e.g., Denhardt's solution, dry milk, salmon sperm DNA, etc.).

"Consensus sequence" refers to a nucleic acid sequence which has been resequenced to resolve uncalled bases, extended using the XL-PCR kit (Perkin-Elmer, Norwalk CT) in the 5' and/or the 3' direction, and resequenced, or which has been assembled from the overlapping sequences of more than one Incyte Clone using a computer program for fragment assembly, such as the GELVIEW fragment assembly system (GCG, Madison WI). Some sequences have been both extended and assembled to produce the consensus sequence.

The term "correlates with expression of a polynucleotide" indicates that the detection of the presence of nucleic acids, the same or related to a nucleic acid sequence encoding PHSP, by northern analysis is indicative of the presence of nucleic acids encoding PHSP in a sample, and

thereby correlates with expression of the transcript from the polynucleotide encoding PHSP.

A "deletion" refers to a change in the amino acid or nucleotide sequence that results in the absence of one or more amino acid residues or nucleotides.

The term "derivative" refers to the chemical modification of a polypeptide sequence, or a
5 polynucleotide sequence. Chemical modifications of a polynucleotide sequence can include, for
example, replacement of hydrogen by an alkyl, acyl, or amino group. A derivative polynucleotide
encodes a polypeptide which retains at least one biological or immunological function of the
natural molecule. A derivative polypeptide is one modified by glycosylation, pegylation, or any
similar process that retains at least one biological or immunological function of the polypeptide
10 from which it was derived.

The term "similarity" refers to a degree of complementarity. There may be partial
similarity or complete similarity. The word "identity" may substitute for the word "similarity." A
partially complementary sequence that at least partially inhibits an identical sequence from
hybridizing to a target nucleic acid is referred to as "substantially similar." The inhibition of
15 hybridization of the completely complementary sequence to the target sequence may be examined
using a hybridization assay (Southern or northern blot, solution hybridization, and the like) under
conditions of reduced stringency. A substantially similar sequence or hybridization probe will
compete for and inhibit the binding of a completely similar (identical) sequence to the target
sequence under conditions of reduced stringency. This is not to say that conditions of reduced
20 stringency are such that non-specific binding is permitted, as reduced stringency conditions
require that the binding of two sequences to one another be a specific (i.e., a selective) interaction.
The absence of non-specific binding may be tested by the use of a second target sequence which
lacks even a partial degree of complementarity (e.g., less than about 30% similarity or identity).
In the absence of non-specific binding, the substantially similar sequence or probe will not
25 hybridize to the second non-complementary target sequence.

The phrases "percent identity" and "% identity" refer to the percentage of sequence
similarity found in a comparison of two or more amino acid or nucleic acid sequences. Percent
identity can be determined electronically, e.g., by using the MEGALIGN program (DNASTAR,
Madison WI) which creates alignments between two or more sequences according to methods
30 selected by the user, e.g., the clustal method. (See, e.g., Higgins, D.G. and P.M. Sharp (1988)
Gene 73:237-244.) The clustal algorithm groups sequences into clusters by examining the
distances between all pairs. The clusters are aligned pairwise and then in groups. The percentage
similarity between two amino acid sequences, e.g., sequence A and sequence B, is calculated by
dividing the length of sequence A, minus the number of gap residues in sequence A, minus the
35 number of gap residues in sequence B, into the sum of the residue matches between sequence A

and sequence B, times one hundred. Gaps of low or of no similarity between the two amino acid sequences are not included in determining percentage similarity. Percent identity between nucleic acid sequences can also be counted or calculated by other methods known in the art, e.g., the Jotun Hein method. (See, e.g., Hein, J. (1990) *Methods Enzymol.* 183:626-645.) Identity between
5 sequences can also be determined by other methods known in the art, e.g., by varying hybridization conditions.

“Human artificial chromosomes” (HACs) are linear microchromosomes which may contain DNA sequences of about 6 kb to 10 Mb in size, and which contain all of the elements required for stable mitotic chromosome segregation and maintenance.

10 The term “humanized antibody” refers to antibody molecules in which the amino acid sequence in the non-antigen binding regions has been altered so that the antibody more closely resembles a human antibody, and still retains its original binding ability.

“Hybridization” refers to any process by which a strand of nucleic acid binds with a complementary strand through base pairing.

15 The term “hybridization complex” refers to a complex formed between two nucleic acid sequences by virtue of the formation of hydrogen bonds between complementary bases. A hybridization complex may be formed in solution (e.g., C_0t or R_0t analysis) or formed between one nucleic acid sequence present in solution and another nucleic acid sequence immobilized on a solid support (e.g., paper, membranes, filters, chips, pins or glass slides, or any other appropriate
20 substrate to which cells or their nucleic acids have been fixed).

The words “insertion” or “addition” refer to changes in an amino acid or nucleotide sequence resulting in the addition of one or more amino acid residues or nucleotides, respectively, to the sequence found in the naturally occurring molecule.

“Immune response” can refer to conditions associated with inflammation, trauma, immune
25 disorders, or infectious or genetic disease, etc. These conditions can be characterized by expression of various factors, e.g., cytokines, chemokines, and other signaling molecules, which may affect cellular and systemic defense systems.

The term “microarray” refers to an arrangement of distinct polynucleotides on a substrate.

The terms “element” or “array element” in a microarray context, refer to hybridizable
30 polynucleotides arranged on the surface of a substrate.

The term “modulate” refers to a change in the activity of PHSP. For example, modulation may cause an increase or a decrease in protein activity, binding characteristics, or any other biological, functional, or immunological properties of PHSP.

The phrases “nucleic acid” or “nucleic acid sequence,” as used herein, refer to a
35 nucleotide, oligonucleotide, polynucleotide, or any fragment thereof. These phrases also refer to

DNA or RNA of genomic or synthetic origin which may be single-stranded or double-stranded and may represent the sense or the antisense strand, to peptide nucleic acid (PNA), or to any DNA-like or RNA-like material. In this context, "fragments" refers to those nucleic acid sequences which, comprise a region of unique polynucleotide sequence that specifically identifies
5 SEQ ID NO:32-62, for example, as distinct from any other sequence in the same genome. For example, a fragment of SEQ ID NO:32-62 is useful in hybridization and amplification technologies and in analogous methods that distinguish SEQ ID NO:32-62 from related polynucleotide sequences. A fragment of SEQ ID NO:32-62 is at least about 15-20 nucleotides in length. The precise length of the fragment of SEQ ID NO:32-62 and the region of SEQ ID
10 NO:32-62 to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment. In some cases, a fragment, when translated, would produce polypeptides retaining some functional characteristic, e.g., antigenicity, or structural domain characteristic, e.g., ATP-binding site, of the full-length polypeptide

The terms "operably associated" or "operably linked" refer to functionally related nucleic
15 acid sequences. A promoter is operably associated or operably linked with a coding sequence if the promoter controls the translation of the encoded polypeptide. While operably associated or operably linked nucleic acid sequences can be contiguous and in the same reading frame, certain genetic elements, e.g., repressor genes, are not contiguously linked to the sequence encoding the polypeptide but still bind to operator sequences that control expression of the polypeptide.

20 The term "oligonucleotide" refers to a nucleic acid sequence of at least about 6 nucleotides to 60 nucleotides, preferably about 15 to 30 nucleotides, and most preferably about 20 to 25 nucleotides, which can be used in PCR amplification or in a hybridization assay or microarray. "Oligonucleotide" is substantially equivalent to the terms "amplimer," "primer," "oligomer," and "probe," as these terms are commonly defined in the art.

25 "Peptide nucleic acid" (PNA) refers to an antisense molecule or anti-gene agent which comprises an oligonucleotide of at least about 5 nucleotides in length linked to a peptide backbone of amino acid residues ending in lysine. The terminal lysine confers solubility to the composition. PNAs preferentially bind complementary single stranded DNA or RNA and stop transcript elongation, and may be pegylated to extend their lifespan in the cell.

30 The term "sample" is used in its broadest sense. A sample suspected of containing nucleic acids encoding PHSP, or fragments thereof, or PHSP itself, may comprise a bodily fluid; an extract from a cell, chromosome, organelle, or membrane isolated from a cell; a cell; genomic DNA, RNA, or cDNA, in solution or bound to a substrate; a tissue; a tissue print; etc.

The terms "specific binding" or "specifically binding" refer to that interaction between a
35 protein or peptide and an agonist, an antibody, or an antagonist. The interaction is dependent upon

the presence of a particular structure of the protein, e.g., the antigenic determinant or epitope, recognized by the binding molecule. For example, if an antibody is specific for epitope "A," the presence of a polypeptide containing the epitope A, or the presence of free unlabeled A, in a reaction containing free labeled A and the antibody will reduce the amount of labeled A that binds
5 to the antibody.

The term "stringent conditions" refers to conditions which permit hybridization between polynucleotides and the claimed polynucleotides. Stringent conditions can be defined by salt concentration, the concentration of organic solvent, e.g., formamide, temperature, and other conditions well known in the art. In particular, stringency can be increased by reducing the
10 concentration of salt, increasing the concentration of formamide, or raising the hybridization temperature.

The term "substantially purified" refers to nucleic acid or amino acid sequences that are removed from their natural environment and are isolated or separated, and are at least about 60% free, preferably about 75% free, and most preferably about 90% free from other components with
15 which they are naturally associated.

A "substitution" refers to the replacement of one or more amino acids or nucleotides by different amino acids or nucleotides, respectively.

"Substrate" refers to any suitable rigid or semi-rigid support including membranes, filters, chips, slides, wafers, fibers, magnetic or nonmagnetic beads, gels, tubing, plates, polymers,
20 microparticles and capillaries. The substrate can have a variety of surface forms, such as wells, trenches, pins, channels and pores, to which polynucleotides or polypeptides are bound.

"Transformation" describes a process by which exogenous DNA enters and changes a recipient cell. Transformation may occur under natural or artificial conditions according to various methods well known in the art, and may rely on any known method for the insertion of
25 foreign nucleic acid sequences into a prokaryotic or eukaryotic host cell. The method for transformation is selected based on the type of host cell being transformed and may include, but is not limited to, viral infection, electroporation, heat shock, lipofection, and particle bombardment. The term "transformed" cells includes stably transformed cells in which the inserted DNA is capable of replication either as an autonomously replicating plasmid or as part of the host
30 chromosome, as well as transiently transformed cells which express the inserted DNA or RNA for limited periods of time.

A "variant" of PHSP polypeptides refers to an amino acid sequence that is altered by one or more amino acid residues. The variant may have "conservative" changes, wherein a substituted amino acid has similar structural or chemical properties (e.g., replacement of leucine with
35 isoleucine). More rarely, a variant may have "nonconservative" changes (e.g., replacement of

glycine with tryptophan). Analogous minor variations may also include amino acid deletions or insertions, or both. Guidance in determining which amino acid residues may be substituted, inserted, or deleted without abolishing biological or immunological activity may be found using computer programs well known in the art, for example, LASERGENE software (DNASTAR).

5 The term "variant," when used in the context of a polynucleotide sequence, may encompass a polynucleotide sequence related to PHSP. This definition may also include, for example, "allelic" (as defined above), "splice," "species," or "polymorphic" variants. A splice variant may have significant identity to a reference molecule, but will generally have a greater or lesser number of polynucleotides due to alternate splicing of exons during mRNA processing. The
10 corresponding polypeptide may possess additional functional domains or an absence of domains. Species variants are polynucleotide sequences that vary from one species to another. The resulting polypeptides generally will have significant amino acid identity relative to each other. A polymorphic variant is a variation in the polynucleotide sequence of a particular gene between individuals of a given species. Polymorphic variants also may encompass "single nucleotide
15 polymorphisms" (SNPs) in which the polynucleotide sequence varies by one base. The presence of SNPs may be indicative of, for example, a certain population, a disease state, or a propensity for a disease state.

THE INVENTION

 The invention is based on the discovery of new human phosphorylation effectors (PHSP),
20 the polynucleotides encoding PHSP, and the use of these compositions for the diagnosis, treatment, or prevention of cell proliferative, immune, and neuronal disorders.

 Table 1 lists the Incyte clones used to assemble full length nucleotide sequences encoding PHSP. Columns 1 and 2 show the sequence identification numbers (SEQ ID NOs) of the polypeptide and nucleotide sequences, respectively. Column 3 shows the clone IDs of the Incyte
25 clones in which nucleic acids encoding each PHSP were identified, and column 4 shows the cDNA libraries from which these clones were isolated. Column 5 shows Incyte clones and their corresponding cDNA libraries. Clones for which cDNA libraries are not indicated were derived from pooled cDNA libraries. The clones in column 5 were used to assemble the consensus nucleotide sequence of each PHSP and are useful as fragments in hybridization technologies.

30 The columns of Table 2 show various properties of each of the polypeptides of the invention: column 1 references the SEQ ID NO and column 2 shows the number of amino acid residues in each polypeptide. Columns 3 and 4 show potential phosphorylation sites and potential glycosylation sites, respectively. Column 5 shows the amino acid residues comprising signature sequences and motifs. Column 6 shows homologous sequences as identified by BLAST analysis,
35 while column 7 shows analytical methods used to identify each polypeptide through sequence

homology and protein motifs.

The columns of Table 3 show the tissue-specificity and diseases, disorders, or conditions associated with nucleotide sequences encoding PHSP. The first column of Table 3 lists the SEQ ID NOs. Column 2 lists tissue categories which express PHSP as a fraction of total tissue categories expressing PHSP. Column 3 lists diseases, disorders, or conditions associated with those tissues expressing PHSP. Column 4 lists the vectors used to subclone the cDNA library.

The columns of Table 4 show descriptions of the tissues used to construct the cDNA libraries from which cDNA clones encoding PHSP were isolated. Column 1 references the SEQ ID NO, column 2 shows the cDNA libraries from which these clones were isolated, and column 3 shows the tissue origins and other descriptive information relevant to the cDNA libraries in column 2.

The following fragments of the nucleotide sequences encoding PHSP are useful, for example, in hybridization or amplification technologies to identify SEQ ID NO:32-62 and to distinguish between SEQ ID NO:32-62 and related polynucleotide sequences. The useful fragments include, the fragment of SEQ ID NO:32 from about nucleotide 81 to about nucleotide 110; the fragment of SEQ ID NO:33 from about nucleotide 323 to about nucleotide 352; the fragment of SEQ ID NO:34 from about nucleotide 83 to about nucleotide 112; the fragment of SEQ ID NO:35 from about nucleotide 524 to about nucleotide 553; the fragment of SEQ ID NO:36 from about nucleotide 275 to about nucleotide 346; the fragment of SEQ ID NO:37 from about nucleotide 1328 to about nucleotide 1396; the fragment of SEQ ID NO:38 from about nucleotide 245 to about nucleotide 304; the fragment of SEQ ID NO:39 from about nucleotide 1253 to about nucleotide 1312; the fragment of SEQ ID NO:41 from about nucleotide 117 to about nucleotide 170; the fragments of SEQ ID NO:42 from about nucleotide 109 to about nucleotide 153, and from about nucleotide 325 to about nucleotide 369; the fragments of SEQ ID NO:43 from about nucleotide 380 to about nucleotide 424, and from about nucleotide 1190 to about nucleotide 1234; the fragment of SEQ ID NO:44 from about nucleotide 1 to about nucleotide 46; the fragment of SEQ ID NO:45 from about nucleotide 533 to about nucleotide 577; the fragments of SEQ ID NO:46 from about nucleotide 109 to about nucleotide 153, and from about nucleotide 379 to about nucleotide 423; the fragment of SEQ ID NO:47 from about nucleotide 1730 to about nucleotide 1774; the fragment of SEQ ID NO:48 from about nucleotide 433 to about nucleotide 477; the fragment of SEQ ID NO:49 from about nucleotide 1117 to about nucleotide 1155; the fragment of SEQ ID NO:50 from about nucleotide 166 to about nucleotide 213; the fragment of SEQ ID NO:51 from about nucleotide 60 to about nucleotide 95; the fragment of SEQ ID NO:52 from about nucleotide 326 to about nucleotide 370; the fragment of SEQ ID NO:53 from about nucleotide 25 to about nucleotide 66; the fragment of SEQ ID NO:54 from about nucleotide 55 to

about nucleotide 102; the fragment of SEQ ID NO:55 from about nucleotide 138 to about nucleotide 167; the fragment of SEQ ID NO:56 from about nucleotide 29 to about nucleotide 58; the fragment of SEQ ID NO:57 from about nucleotide 455 to about nucleotide 484; the fragment of SEQ ID NO:58 from about nucleotide 226 to about nucleotide 255; the fragment of SEQ ID NO:59 from about nucleotide 557 to about nucleotide 598; the fragment of SEQ ID NO:60 from about nucleotide 284 to about nucleotide 325; the fragment of SEQ ID NO:61 from about nucleotide 1043 to about nucleotide 1090; and the fragment of SEQ ID NO:62 from about nucleotide 84 to about nucleotide 132. The polypeptides encoded by the fragments of SEQ ID NO:32-62 are useful, for example, as immunogenic peptides.

10 The invention also encompasses PHSP variants. A preferred PHSP variant is one which has at least about 80%, more preferably at least about 90%, and most preferably at least about 95% amino acid sequence identity to the PHSP amino acid sequence, and which contains at least one functional or structural characteristic of PHSP.

15 The invention also encompasses polynucleotides which encode PHSP. In a particular embodiment, the invention encompasses a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:32-62, which encodes PHSP.

20 The invention also encompasses a variant of a polynucleotide sequence encoding PHSP. In particular, such a variant polynucleotide sequence will have at least about 80%, more preferably at least about 85%, and most preferably at least about 95% polynucleotide sequence identity to the polynucleotide sequence encoding PHSP. A particular aspect of the invention encompasses a variant of a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:32-62 which has at least about 80%, more preferably at least about 85%, and most preferably at least about 95% polynucleotide sequence identity to a nucleic acid sequence selected from the group consisting of SEQ ID NO:32-62. Any one of the polynucleotide variants described above can encode an amino acid sequence which contains at least one functional or structural characteristic of PHSP.

25 It will be appreciated by those skilled in the art that as a result of the degeneracy of the genetic code, a multitude of polynucleotide sequences encoding PHSP, some bearing minimal similarity to the polynucleotide sequences of any known and naturally occurring gene, may be produced. Thus, the invention contemplates each and every possible variation of polynucleotide sequence that could be made by selecting combinations based on possible codon choices. These combinations are made in accordance with the standard triplet genetic code as applied to the polynucleotide sequence of naturally occurring PHSP, and all such variations are to be considered as being specifically disclosed.

30 Although nucleotide sequences which encode PHSP and its variants are preferably capable of hybridizing to the nucleotide sequence of the naturally occurring PHSP under appropriately selected conditions of stringency, it may be advantageous to produce nucleotide sequences encoding

PHSP or its derivatives possessing a substantially different codon usage, e.g., inclusion of non-naturally occurring codons. Codons may be selected to increase the rate at which expression of the peptide occurs in a particular prokaryotic or eukaryotic host in accordance with the frequency with which particular codons are utilized by the host. Other reasons for substantially altering the nucleotide sequence encoding PHSP and its derivatives without altering the encoded amino acid sequences include the production of RNA transcripts having more desirable properties, such as a greater half-life, than transcripts produced from the naturally occurring sequence.

The invention also encompasses production of DNA sequences which encode PHSP and PHSP derivatives, or fragments thereof, entirely by synthetic chemistry. After production, the synthetic sequence may be inserted into any of the many available expression vectors and cell systems using reagents well known in the art. Moreover, synthetic chemistry may be used to introduce mutations into a sequence encoding PHSP or any fragment thereof.

Also encompassed by the invention are polynucleotide sequences that are capable of hybridizing to the claimed polynucleotide sequences, and, in particular, to those shown in SEQ ID NO:32-62 and fragments thereof under various conditions of stringency. (See, e.g., Wahl, G.M. and S.L. Berger (1987) *Methods Enzymol.* 152:399-407; Kimmel, A.R. (1987) *Methods Enzymol.* 152:507-511.) For example, stringent salt concentration will ordinarily be less than about 750 mM NaCl and 75 mM trisodium citrate, preferably less than about 500 mM NaCl and 50 mM trisodium citrate, and most preferably less than about 250 mM NaCl and 25 mM trisodium citrate. Low stringency hybridization can be obtained in the absence of organic solvent, e.g., formamide, while high stringency hybridization can be obtained in the presence of at least about 35% formamide, and most preferably at least about 50% formamide. Stringent temperature conditions will ordinarily include temperatures of at least about 30°C, more preferably of at least about 37°C, and most preferably of at least about 42°C. Varying additional parameters, such as hybridization time, the concentration of detergent, e.g., sodium dodecyl sulfate (SDS), and the inclusion or exclusion of carrier DNA, are well known to those skilled in the art. Various levels of stringency are accomplished by combining these various conditions as needed. In a preferred embodiment, hybridization will occur at 30°C in 750 mM NaCl, 75 mM trisodium citrate, and 1% SDS. In a more preferred embodiment, hybridization will occur at 37°C in 500 mM NaCl, 50 mM trisodium citrate, 1% SDS, 35% formamide, and 100 µg/ml denatured salmon sperm DNA (ssDNA). In a most preferred embodiment, hybridization will occur at 42°C in 250 mM NaCl, 25 mM trisodium citrate, 1% SDS, 50 % formamide, and 200 µg/ml ssDNA. Useful variations on these conditions will be readily apparent to those skilled in the art.

The washing steps which follow hybridization can also vary in stringency. Wash stringency conditions can be defined by salt concentration and by temperature. As above, wash stringency can

be increased by decreasing salt concentration or by increasing temperature. For example, stringent salt concentration for the wash steps will preferably be less than about 30 mM NaCl and 3 mM trisodium citrate, and most preferably less than about 15 mM NaCl and 1.5 mM trisodium citrate. Stringent temperature conditions for the wash steps will ordinarily include temperature of at least
5 about 25°C, more preferably of at least about 42°C, and most preferably of at least about 68°C. In a preferred embodiment, wash steps will occur at 25°C in 30 mM NaCl, 3 mM trisodium citrate, and 0.1% SDS. In a more preferred embodiment, wash steps will occur at 42°C in 15 mM NaCl, 1.5 mM trisodium citrate, and 0.1% SDS. In a most preferred embodiment, wash steps will occur at 68°C in 15 mM NaCl, 1.5 mM trisodium citrate, and 0.1% SDS. Additional variations on these conditions will
10 be readily apparent to those skilled in the art.

Methods for DNA sequencing are well known in the art and may be used to practice any of the embodiments of the invention. The methods may employ such enzymes as the Klenow fragment of DNA polymerase I, SEQUENASE (US Biochemical, Cleveland OH), Taq polymerase (Perkin-Elmer), thermostable T7 polymerase (Amersham Pharmacia Biotech, Piscataway NJ), or combinations
15 of polymerases and proofreading exonucleases such as those found in the ELONGASE amplification system (Life Technologies, Gaithersburg MD). Preferably, sequence preparation is automated with machines such as the MICROLAB 2200 (Hamilton, Reno NV), Peltier thermal cycler 200 (PTC200; MJ Research, Watertown MA) and the ABI CATALYST 800 (Perkin-Elmer). Sequencing is then carried out using the ABI 373 or 377 DNA sequencing systems (Perkin-Elmer), or the MEGABACE
20 1000 DNA sequencing system (Molecular Dynamics, Sunnyvale CA), or other systems known in the art. The resulting sequences are analyzed using a variety of algorithms which are well known in the art. (See, e.g., Ausubel, F.M. (1997) Short Protocols in Molecular Biology, John Wiley & Sons, New York NY, unit 7.7; Meyers, R.A. (1995) Molecular Biology and Biotechnology, Wiley VCH, New York NY, pp. 856-853.)

25 The nucleic acid sequences encoding PHSP may be extended utilizing a partial nucleotide sequence and employing various PCR-based methods known in the art to detect upstream sequences, such as promoters and regulatory elements. For example, one method which may be employed, restriction-site PCR, uses universal and nested primers to amplify unknown sequence from genomic DNA within a cloning vector. (See, e.g., Sarkar, G. (1993) PCR Methods Applic. 2:318-322.)
30 Another method, inverse PCR, uses primers that extend in divergent directions to amplify unknown sequence from a circularized template. The template is derived from restriction fragments comprising a known genomic locus and surrounding sequences. (See, e.g., Triglia, T. et al. (1988) Nucleic Acids Res. 16:8186.) A third method, capture PCR, involves PCR amplification of DNA fragments adjacent to known sequences in human and yeast artificial chromosome DNA. (See, e.g., Lagerstrom, M. et
35 al. (1991) PCR Methods Applic. 1:111-119.) In this method, multiple restriction enzyme digestions

and ligations may be used to insert an engineered double-stranded sequence into a region of unknown sequence before performing PCR. Other methods which may be used to retrieve unknown sequences are known in the art. (See, e.g., Parker, J.D. et al. (1991) *Nucleic Acids Res.* 19:3055-306). Additionally, one may use PCR, nested primers, and PROMOTERFINDER libraries (Clontech, Palo Alto CA) to walk genomic DNA. This procedure avoids the need to screen libraries and is useful in finding intron/exon junctions. For all PCR-based methods, primers may be designed using commercially available software, such as OLIGO 4.06 primer analysis software (National Biosciences, Plymouth MN) or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the template at temperatures of about 68°C to 72°C.

When screening for full-length cDNAs, it is preferable to use libraries that have been size-selected to include larger cDNAs. In addition, random-primed libraries, which often include sequences containing the 5' regions of genes, are preferable for situations in which an oligo d(T) library does not yield a full-length cDNA. Genomic libraries may be useful for extension of sequence into 5' non-transcribed regulatory regions.

Capillary electrophoresis systems which are commercially available may be used to analyze the size or confirm the nucleotide sequence of sequencing or PCR products. In particular, capillary sequencing may employ flowable polymers for electrophoretic separation, four different nucleotide-specific, laser-stimulated fluorescent dyes, and a charge coupled device camera for detection of the emitted wavelengths. Output/light intensity may be converted to electrical signal using appropriate software (e.g., GENOTYPER and SEQUENCE NAVIGATOR, Perkin-Elmer), and the entire process from loading of samples to computer analysis and electronic data display may be computer controlled. Capillary electrophoresis is especially preferable for sequencing small DNA fragments which may be present in limited amounts in a particular sample.

In another embodiment of the invention, polynucleotide sequences or fragments thereof which encode PHSP may be cloned in recombinant DNA molecules that direct expression of PHSP, or fragments or functional equivalents thereof, in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences which encode substantially the same or a functionally equivalent amino acid sequence may be produced and used to express PHSP.

The nucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter PHSP-encoding sequences for a variety of purposes including, but not limited to, modification of the cloning, processing, and/or expression of the gene product. DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. For example, oligonucleotide-mediated site-directed mutagenesis may be used to introduce mutations that create new restriction

sites, alter glycosylation patterns, change codon preference, produce splice variants, and so forth.

In another embodiment, sequences encoding PHSP may be synthesized, in whole or in part, using chemical methods well known in the art. (See, e.g., Caruthers, M.H. et al. (1980) Nucl. Acids Res. Symp. Ser. 215-223, and Horn, T. et al. (1980) Nucl. Acids Res. Symp. Ser. 225-232.)

5 Alternatively, PHSP itself or a fragment thereof may be synthesized using chemical methods. For example, peptide synthesis can be performed using various solid-phase techniques. (See, e.g., Roberge, J.Y. et al. (1995) Science 269:202-204.) Automated synthesis may be achieved using the ABI 431A Peptide Synthesizer (Perkin-Elmer). Additionally, the amino acid sequence of PHSP, or any part thereof, may be altered during direct synthesis and/or combined with sequences from other
10 proteins, or any part thereof, to produce a variant polypeptide.

The peptide may be substantially purified by preparative high performance liquid chromatography. (See, e.g., Chiez, R.M. and F.Z. Regnier (1990) Methods Enzymol. 182:392-421.)

The composition of the synthetic peptides may be confirmed by amino acid analysis or by sequencing.

(See, e.g., Creighton, T. (1984) Proteins, Structures and Molecular Properties, WH Freeman, New
15 York NY.)

In order to express a biologically active PHSP, the nucleotide sequences encoding PHSP or derivatives thereof may be inserted into an appropriate expression vector, i.e., a vector which contains the necessary elements for transcriptional and translational control of the inserted coding sequence in a suitable host. These elements include regulatory sequences, such as enhancers, constitutive and
20 inducible promoters, and 5' and 3' untranslated regions in the vector and in polynucleotide sequences encoding PHSP. Such elements may vary in their strength and specificity. Specific initiation signals may also be used to achieve more efficient translation of sequences encoding PHSP. Such signals include the ATG initiation codon and adjacent sequences, e.g. the Kozak sequence. In cases where sequences encoding PHSP and its initiation codon and upstream regulatory sequences are inserted into
25 the appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a fragment thereof, is inserted, exogenous translational control signals including an in-frame ATG initiation codon should be provided by the vector. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion
30 of enhancers appropriate for the particular host cell system used. (See, e.g., Scharf, D. et al. (1994) Results Probl. Cell Differ. 20:125-162.)

Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding PHSP and appropriate transcriptional and translational control elements. These methods include in vitro recombinant DNA techniques, synthetic techniques, and
35 in vivo genetic recombination. (See, e.g., Sambrook, J. et al. (1989) Molecular Cloning, A Laboratory

Manual, Cold Spring Harbor Press, Plainview NY, ch. 4, 8, and 16-17; Ausubel, F.M. et al. (1995) Current Protocols in Molecular Biology, John Wiley & Sons, New York NY, ch. 9, 13, and 16.)

A variety of expression vector/host systems may be utilized to contain and express sequences encoding PHSP. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with viral expression vectors (e.g., baculovirus); plant cell systems transformed with viral expression vectors (e.g., cauliflower mosaic virus, CaMV, or tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids); or animal cell systems. The invention is not limited by the host cell employed.

10 In bacterial systems, a number of cloning and expression vectors may be selected depending upon the use intended for polynucleotide sequences encoding PHSP. For example, routine cloning, subcloning, and propagation of polynucleotide sequences encoding PHSP can be achieved using a multifunctional E. coli vector such as PBLUESCRIPT (Stratagene, La Jolla CA) or pSPORT1 plasmid (Life Technologies). Ligation of sequences encoding PHSP into the vector's multiple cloning site
15 disrupts the *lacZ* gene, allowing a colorimetric screening procedure for identification of transformed bacteria containing recombinant molecules. In addition, these vectors may be useful for in vitro transcription, dideoxy sequencing, single strand rescue with helper phage, and creation of nested deletions in the cloned sequence. (See, e.g., Van Heeke, G. and S.M. Schuster (1989) *J. Biol. Chem.* 264:5503-5509.) When large quantities of PHSP are needed, e.g. for the production of antibodies,
20 vectors which direct high level expression of PHSP may be used. For example, vectors containing the strong, inducible T5 or T7 bacteriophage promoter may be used.

Yeast expression systems may be used for production of PHSP. A number of vectors containing constitutive or inducible promoters, such as alpha factor, alcohol oxidase, and PGH, may be used in the yeast Saccharomyces cerevisiae or Pichia pastoris. In addition, such vectors direct
25 either the secretion or intracellular retention of expressed proteins and enable integration of foreign sequences into the host genome for stable propagation. (See, e.g., Ausubel, 1995, supra; Grant et al. (1987) *Methods Enzymol.* 153:516-54; and Scorer, C. A. et al. (1994) *Bio/Technology* 12:181-184.)

Plant systems may also be used for expression of PHSP. Transcription of sequences encoding PHSP may be driven viral promoters, e.g., the 35S and 19S promoters of CaMV used alone or in
30 combination with the omega leader sequence from TMV (Takamatsu, N. (1987) *EMBO J.* 6:307-311). Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used. (See, e.g., Coruzzi, G. et al. (1984) *EMBO J.* 3:1671-1680; Broglie, R. et al. (1984) *Science* 224:838-843; and Winter, J. et al. (1991) *Results Probl. Cell Differ.* 17:85-105.) These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. (See,
35 e.g., The McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York NY,

pp. 191-196.)

In mammalian cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, sequences encoding PHSP may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain infective virus which expresses PHSP in host cells. (See, e.g., Logan, J. and T. Shenk (1984) Proc. Natl. Acad. Sci. 81:3655-3659.) In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells. SV40 or EBV-based vectors may also be used for high-level protein expression.

Human artificial chromosomes (HACs) may also be employed to deliver larger fragments of DNA than can be contained in and expressed from a plasmid. HACs of about 6 kb to 10 Mb are constructed and delivered via conventional delivery methods (liposomes, polycationic amino polymers, or vesicles) for therapeutic purposes. (See, e.g., Harrington, J.J. et al. (1997) Nat Genet. 15:345-355.)

For long term production of recombinant proteins in mammalian systems, stable expression of PHSP in cell lines is preferred. For example, sequences encoding PHSP can be transformed into cell lines using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for about 1 to 2 days in enriched media before being switched to selective media. The purpose of the selectable marker is to confer resistance to a selective agent, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be propagated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase and adenine phosphoribosyltransferase genes, for use in *tk* or *apr* cells, respectively. (See, e.g., Wigler, M. et al. (1977) Cell 11:223-232; Lowy, I. et al. (1980) Cell 22:817-823.) Also, antimetabolite, antibiotic, or herbicide resistance can be used as the basis for selection. For example, *dhfr* confers resistance to methotrexate; *neo* confers resistance to the aminoglycosides, neomycin and G-418; and *als* or *pat* confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively. (See, e.g., Wigler, M. et al. (1980) Proc. Natl. Acad. Sci. 77:3567-3570; Colbere-Garapin, F. et al. (1981) J. Mol. Biol. 150:1-14.) Additional selectable genes have been described, e.g., *trpB* and *hisD*, which alter cellular requirements for metabolites. (See, e.g., Hartman, S.C. and R.C. Mulligan (1988) Proc. Natl. Acad. Sci. 85:8047-8051.) Visible markers, e.g., anthocyanins, green fluorescent proteins (GFP; Clontech), β glucuronidase and its substrate β -glucuronide, or luciferase and its substrate luciferin may

be used. These markers can be used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system. (See, e.g., Rhodes, C.A. (1995) *Methods Mol. Biol.* 55:121-131.)

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, the presence and expression of the gene may need to be confirmed. For example, if the sequence encoding PHSP is inserted within a marker gene sequence, transformed cells containing sequences encoding PHSP can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a sequence encoding PHSP under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

In general, host cells that contain the nucleic acid sequence encoding PHSP and that express PHSP may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations, PCR amplification, and protein bioassay or immunoassay techniques which include membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein sequences.

Immunological methods for detecting and measuring the expression of PHSP using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on PHSP is preferred, but a competitive binding assay may be employed. These and other assays are well known in the art. (See, e.g., Hampton, R. et al. (1990) Serological Methods, a Laboratory Manual, APS Press, St Paul MN, Sect. IV; Coligan, J. E. et al. (1997) Current Protocols in Immunology, Greene Pub. Associates and Wiley-Interscience, New York NY; and Pound, J.D. (1998) Immunochemical Protocols, Humana Press, Totowa NJ).

A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides encoding PHSP include oligolabeling, nick translation, end-labeling, or PCR amplification using a labeled nucleotide. Alternatively, the sequences encoding PHSP, or any fragments thereof, may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes *in vitro* by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits, such as those provided by Amersham Pharmacia Biotech, Promega (Madison WI), and US Biochemical. Suitable reporter molecules or labels which may be used for

ease of detection include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents, as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with nucleotide sequences encoding PHSP may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein
5 produced by a transformed cell may be secreted or retained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides which encode PHSP may be designed to contain signal sequences which direct secretion of PHSP through a prokaryotic or eukaryotic cell membrane.

In addition, a host cell strain may be chosen for its ability to modulate expression of the
10 inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" form of the protein may also be used to specify protein targeting, folding, and/or activity. Different host cells which have specific cellular machinery and characteristic mechanisms for post-translational
15 activities (e.g., CHO, HeLa, MDCK, HEK293, and WI38), are available from the American Type Culture Collection (ATCC, Bethesda MD) and may be chosen to ensure the correct modification and processing of the foreign protein.

In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences encoding PHSP may be ligated to a heterologous sequence resulting in translation of a
20 fusion protein in any of the aforementioned host systems. For example, a chimeric PHSP protein containing a heterologous moiety that can be recognized by a commercially available antibody may facilitate the screening of peptide libraries for inhibitors of PHSP activity. Heterologous protein and peptide moieties may also facilitate purification of fusion proteins using commercially available affinity matrices. Such moieties include, but are not limited to, glutathione S-transferase (GST),
25 maltose binding protein (MBP), thioredoxin (Trx), calmodulin binding peptide (CBP), 6-His, FLAG, *c-myc*, and hemagglutinin (HA). GST, MBP, Trx, CBP, and 6-His enable purification of their cognate fusion proteins on immobilized glutathione, maltose, phenylarsine oxide, calmodulin, and metal-chelate resins, respectively. FLAG, *c-myc*, and hemagglutinin (HA) enable immunoaffinity
30 purification of fusion proteins using commercially available monoclonal and polyclonal antibodies that specifically recognize these epitope tags. A fusion protein may also be engineered to contain a proteolytic cleavage site located between the PHSP encoding sequence and the heterologous protein sequence, so that PHSP may be cleaved away from the heterologous moiety following purification. Methods for fusion protein expression and purification are discussed in Ausubel (1995, supra, ch 10). A variety of commercially available kits may also be used to facilitate expression and purification of
35 fusion proteins.

In a further embodiment of the invention, synthesis of radiolabeled PHSP may be achieved in vitro using the TNT rabbit reticulocyte lysate or wheat germ extract systems (Promega). These systems couple transcription and translation of protein-coding sequences operably associated with the T7, T3, or SP6 promoters. Translation takes place in the presence of a radiolabeled amino acid precursor, preferably ^{35}S -methionine.

Fragments of PHSP may be produced not only by recombinant production, but also by direct peptide synthesis using solid-phase techniques. (See, e.g., Creighton, supra, pp. 55-60.) Protein synthesis may be performed by manual techniques or by automation. Automated synthesis may be achieved, for example, using the ABI 431A Peptide Synthesizer (Perkin-Elmer). Various fragments of PHSP may be synthesized separately and then combined to produce the full length molecule.

THERAPEUTICS

Chemical and structural similarity, e.g., in the context of sequences and motifs, exists between regions of PHSP and protein phosphatases. In addition, the expression of PHSP is closely associated with reproductive tissue, nervous tissue, gastrointestinal tissue, cell proliferation, cancer, inflammation, and immune response. Therefore, PHSP appears to play a role in cell proliferative, immune, and neuronal disorders. In the treatment of disorders associated with increased PHSP expression or activity, it is desirable to decrease the expression or activity of PHSP. In the treatment of disorders associated with decreased PHSP expression or activity, it is desirable to increase the expression or activity of PHSP.

Therefore, in one embodiment, PHSP or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of PHSP. Examples of such disorders include, but are not limited to, a cell proliferative disorder, such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, and cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus; an immune disorder, such as acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia with lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis,

hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner's syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, viral, bacterial, fungal, parasitic, protozoal, and helminthic infections, and trauma; and a neuronal disorder, such as akathisia, Alzheimer's disease, amnesia, amyotrophic lateral sclerosis, bipolar disorder, catatonia, dementia, depression, diabetic neuropathy, Down's syndrome, tardive dyskinesia, dystonias, epilepsy, Huntington's disease, peripheral neuropathy, multiple sclerosis, neurofibromatosis, Parkinson's disease, paranoid psychoses, postherpetic neuralgia, schizophrenia, and Tourette's disorder.

In another embodiment, a vector capable of expressing PHSP or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of PHSP including, but not limited to, those described above.

In a further embodiment, a pharmaceutical composition comprising a substantially purified PHSP in conjunction with a suitable pharmaceutical carrier may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of PHSP including, but not limited to, those provided above.

In still another embodiment, an agonist which modulates the activity of PHSP may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of PHSP including, but not limited to, those listed above.

In a further embodiment, an antagonist of PHSP may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of PHSP. Examples of such disorders include, but are not limited to, those described above. In one aspect, an antibody which specifically binds PHSP may be used directly as an antagonist or indirectly as a targeting or delivery mechanism for bringing a pharmaceutical agent to cells or tissue which express PHSP.

In an additional embodiment, a vector expressing the complement of the polynucleotide encoding PHSP may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of PHSP including, but not limited to, those described above.

In other embodiments, any of the proteins, antagonists, antibodies, agonists, complementary sequences, or vectors of the invention may be administered in combination with other appropriate therapeutic agents. Selection of the appropriate agents for use in combination therapy may be made by one of ordinary skill in the art, according to conventional pharmaceutical principles. The combination of therapeutic agents may act synergistically to effect the treatment or prevention of the various disorders described above. Using this approach, one may be able to achieve therapeutic efficacy with lower dosages of each agent, thus reducing the potential for adverse side effects.

An antagonist of PHSP may be produced using methods which are generally known in the art. In particular, purified PHSP may be used to produce antibodies or to screen libraries of pharmaceutical agents to identify those which specifically bind PHSP. Antibodies to PHSP may also be generated using methods that are well known in the art. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, and single chain antibodies, Fab fragments, and fragments produced by a Fab expression library. Neutralizing antibodies (i.e., those which inhibit dimer formation) are especially preferred for therapeutic use.

For the production of antibodies, various hosts including goats, rabbits, rats, mice, humans, and others may be immunized by injection with PHSP or with any fragment or oligopeptide thereof which has immunogenic properties. Depending on the host species, various adjuvants may be used to increase immunological response. Such adjuvants include, but are not limited to, Freund's, mineral gels such as aluminum hydroxide, and surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, KLH, and dinitrophenol. Among adjuvants used in humans, BCG (bacilli Calmette-Guerin) and Corynebacterium parvum are especially preferable.

It is preferred that the oligopeptides, peptides, or fragments used to induce antibodies to PHSP have an amino acid sequence consisting of at least about 5 amino acids, and, more preferably, of at least about 10 amino acids. It is also preferable that these oligopeptides, peptides, or fragments are identical to a portion of the amino acid sequence of the natural protein and contain the entire amino acid sequence of a small, naturally occurring molecule. Short stretches of PHSP amino acids may be fused with those of another protein, such as KLH, and antibodies to the chimeric molecule may be produced.

Monoclonal antibodies to PHSP may be prepared using any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique, the human B-cell hybridoma technique, and the EBV-hybridoma technique. (See, e.g., Kohler, G. et al. (1975) *Nature* 256:495-497; Kozbor, D. et al. (1985) *J. Immunol. Methods* 81:31-42; Cote, R.J. et al. (1983) *Proc. Natl. Acad. Sci.* 80:2026-2030; and Cole, S.P. et al. (1984) *Mol. Cell Biol.* 62:109-120.)

In addition, techniques developed for the production of "chimeric antibodies," such as the splicing of mouse antibody genes to human antibody genes to obtain a molecule with appropriate antigen specificity and biological activity, can be used. (See, e.g., Morrison, S.L. et al. (1984) *Proc. Natl. Acad. Sci.* 81:6851-6855; Neuberger, M.S. et al. (1984) *Nature* 312:604-608; and Takeda, S. et al. (1985) *Nature* 314:452-454.) Alternatively, techniques described for the production of single chain antibodies may be adapted, using methods known in the art, to produce PHSP-specific single chain antibodies. Antibodies with related specificity, but of distinct idiotypic composition, may be generated by chain shuffling from random combinatorial immunoglobulin libraries. (See, e.g., Burton

D.R. (1991) Proc. Natl. Acad. Sci. 88:10134-10137.)

Antibodies may also be produced by inducing in vivo production in the lymphocyte population or by screening immunoglobulin libraries or panels of highly specific binding reagents as disclosed in the literature. (See, e.g., Orlandi, R. et al. (1989) Proc. Natl. Acad. Sci. 86: 3833-3837;

5 Winter, G. et al. (1991) Nature 349:293-299.)

Antibody fragments which contain specific binding sites for PHSP may also be generated. For example, such fragments include, but are not limited to, F(ab')₂ fragments produced by pepsin digestion of the antibody molecule and Fab fragments generated by reducing the disulfide bridges of the F(ab')₂ fragments. Alternatively, Fab expression libraries may be constructed to allow rapid and
10 easy identification of monoclonal Fab fragments with the desired specificity. (See, e.g., Huse, W.D. et al. (1989) Science 246:1275-1281.)

Various immunoassays may be used for screening to identify antibodies having the desired specificity. Numerous protocols for competitive binding or immunoradiometric assays using either polyclonal or monoclonal antibodies with established specificities are well known in the art. Such
15 immunoassays typically involve the measurement of complex formation between PHSP and its specific antibody. A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering PHSP epitopes is preferred, but a competitive binding assay may also be employed (Pound, supra).

Various methods such as Scatchard analysis in conjunction with radioimmunoassay
20 techniques may be used to assess the affinity of antibodies for PHSP. Affinity is expressed as an association constant, K_a , which is defined as the molar concentration of PHSP-antibody complex divided by the molar concentrations of free antigen and free antibody under equilibrium conditions. The K_a determined for a preparation of polyclonal antibodies, which are heterogeneous in their affinities for multiple PHSP epitopes, represents the average affinity, or avidity, of the antibodies for
25 PHSP. The K_a determined for a preparation of monoclonal antibodies, which are monospecific for a particular PHSP epitope, represents a true measure of affinity. High-affinity antibody preparations with K_a ranging from about 10^9 to 10^{12} L/mole are preferred for use in immunoassays in which the PHSP-antibody complex must withstand rigorous manipulations. Low-affinity antibody preparations with K_a ranging from about 10^6 to 10^7 L/mole are preferred for use in immunopurification and similar
30 procedures which ultimately require dissociation of PHSP, preferably in active form, from the antibody (Catty, D. (1988) Antibodies, Volume I: A Practical Approach, IRL Press, Washington, DC; Liddell, J. E. and Cryer, A. (1991) A Practical Guide to Monoclonal Antibodies, John Wiley & Sons, New York NY).

The titer and avidity of polyclonal antibody preparations may be further evaluated to
35 determine the quality and suitability of such preparations for certain downstream applications. For

example, a polyclonal antibody preparation containing at least 1-2 mg specific antibody/ml, preferably 5-10 mg specific antibody/ml, is preferred for use in procedures requiring precipitation of PHSP-antibody complexes. Procedures for evaluating antibody specificity, titer, and avidity, and guidelines for antibody quality and usage in various applications, are generally available. (See, e.g., Catty, supra,
5 and Coligan et al. supra.)

In another embodiment of the invention, the polynucleotides encoding PHSP, or any fragment or complement thereof, may be used for therapeutic purposes. In one aspect, the complement of the polynucleotide encoding PHSP may be used in situations in which it would be desirable to block the transcription of the mRNA. In particular, cells may be transformed with sequences complementary
10 to polynucleotides encoding PHSP. Thus, complementary molecules or fragments may be used to modulate PHSP activity, or to achieve regulation of gene function. Such technology is now well known in the art, and sense or antisense oligonucleotides or larger fragments can be designed from various locations along the coding or control regions of sequences encoding PHSP.

Expression vectors derived from retroviruses, adenoviruses, or herpes or vaccinia viruses, or
15 from various bacterial plasmids, may be used for delivery of nucleotide sequences to the targeted organ, tissue, or cell population. Methods which are well known to those skilled in the art can be used to construct vectors to express nucleic acid sequences complementary to the polynucleotides encoding PHSP. (See, e.g., Sambrook, supra; Ausubel, 1995, supra.)

Genes encoding PHSP can be turned off by transforming a cell or tissue with expression
20 vectors which express high levels of a polynucleotide, or fragment thereof, encoding PHSP. Such constructs may be used to introduce untranslatable sense or antisense sequences into a cell. Even in the absence of integration into the DNA, such vectors may continue to transcribe RNA molecules until they are disabled by endogenous nucleases. Transient expression may last for a month or more with a non-replicating vector, and may last even longer if appropriate replication elements are part of the
25 vector system.

As mentioned above, modifications of gene expression can be obtained by designing complementary sequences or antisense molecules (DNA, RNA, or PNA) to the control, 5', or regulatory regions of the gene encoding PHSP. Oligonucleotides derived from the transcription initiation site, e.g., between about positions -10 and +10 from the start site, are preferred. Similarly,
30 inhibition can be achieved using triple helix base-pairing methodology. Triple helix pairing is useful because it causes inhibition of the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors, or regulatory molecules. Recent therapeutic advances using triplex DNA have been described in the literature. (See, e.g., Gee, J.E. et al. (1994) in Huber, B.E. and B.I. Carr, Molecular and Immunologic Approaches, Futura Publishing, Mt. Kisco NY, pp. 163-177.) A
35 complementary sequence or antisense molecule may also be designed to block translation of mRNA

by preventing the transcript from binding to ribosomes.

Ribozymes, enzymatic RNA molecules, may also be used to catalyze the specific cleavage of RNA. The mechanism of ribozyme action involves sequence-specific hybridization of the ribozyme molecule to complementary target RNA, followed by endonucleolytic cleavage. For example, engineered hammerhead motif ribozyme molecules may specifically and efficiently catalyze endonucleolytic cleavage of sequences encoding PHSP.

Specific ribozyme cleavage sites within any potential RNA target are initially identified by scanning the target molecule for ribozyme cleavage sites, including the following sequences: GUA, GUU, and GUC. Once identified, short RNA sequences of between 15 and 20 ribonucleotides, corresponding to the region of the target gene containing the cleavage site, may be evaluated for secondary structural features which may render the oligonucleotide inoperable. The suitability of candidate targets may also be evaluated by testing accessibility to hybridization with complementary oligonucleotides using ribonuclease protection assays.

Complementary ribonucleic acid molecules and ribozymes of the invention may be prepared by any method known in the art for the synthesis of nucleic acid molecules. These include techniques for chemically synthesizing oligonucleotides such as solid phase phosphoramidite chemical synthesis. Alternatively, RNA molecules may be generated by *in vitro* and *in vivo* transcription of DNA sequences encoding PHSP. Such DNA sequences may be incorporated into a wide variety of vectors with suitable RNA polymerase promoters such as T7 or SP6. Alternatively, these cDNA constructs that synthesize complementary RNA, constitutively or inducibly, can be introduced into cell lines, cells, or tissues.

RNA molecules may be modified to increase intracellular stability and half-life. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends of the molecule, or the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages within the backbone of the molecule. This concept is inherent in the production of PNAs and can be extended in all of these molecules by the inclusion of nontraditional bases such as inosine, queosine, and wybutosine, as well as acetyl-, methyl-, thio-, and similarly modified forms of adenine, cytidine, guanine, thymine, and uridine which are not as easily recognized by endogenous endonucleases.

Many methods for introducing vectors into cells or tissues are available and equally suitable for use *in vivo*, *in vitro*, and *ex vivo*. For *ex vivo* therapy, vectors may be introduced into stem cells taken from the patient and clonally propagated for autologous transplant back into that same patient. Delivery by transfection, by liposome injections, or by polycationic amino polymers may be achieved using methods which are well known in the art. (See, e.g., Goldman, C.K. et al. (1997) Nature Biotechnology 15:462-466.)

Any of the therapeutic methods described above may be applied to any subject in need of such

therapy, including, for example, mammals such as dogs, cats, cows, horses, rabbits, monkeys, and most preferably, humans.

An additional embodiment of the invention relates to the administration of a pharmaceutical or sterile composition, in conjunction with a pharmaceutically acceptable carrier, for any of the therapeutic effects discussed above. Such pharmaceutical compositions may consist of PHSP, antibodies to PHSP, and mimetics, agonists, antagonists, or inhibitors of PHSP. The compositions may be administered alone or in combination with at least one other agent, such as a stabilizing compound, which may be administered in any sterile, biocompatible pharmaceutical carrier including, but not limited to, saline, buffered saline, dextrose, and water. The compositions may be administered to a patient alone, or in combination with other agents, drugs, or hormones.

The pharmaceutical compositions utilized in this invention may be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, or rectal means.

In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically-acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing, Easton PA).

Pharmaceutical compositions for oral administration can be formulated using pharmaceutically acceptable carriers well known in the art in dosages suitable for oral administration. Such carriers enable the pharmaceutical compositions to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for ingestion by the patient.

Pharmaceutical preparations for oral use can be obtained through combining active compounds with solid excipient and processing the resultant mixture of granules (optionally, after grinding) to obtain tablets or dragee cores. Suitable auxiliaries can be added, if desired. Suitable excipients include carbohydrate or protein fillers, such as sugars, including lactose, sucrose, mannitol, and sorbitol; starch from corn, wheat, rice, potato, or other plants; cellulose, such as methyl cellulose, hydroxypropylmethyl-cellulose, or sodium carboxymethylcellulose; gums, including arabic and tragacanth; and proteins, such as gelatin and collagen. If desired, disintegrating or solubilizing agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, and alginic acid or a salt thereof, such as sodium alginate.

Dragee cores may be used in conjunction with suitable coatings, such as concentrated sugar solutions, which may also contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures.

Dyestuffs or pigments may be added to the tablets or dragee coatings for product identification or to characterize the quantity of active compound, i.e., dosage.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a coating, such as glycerol or sorbitol.

- 5 Push-fit capsules can contain active ingredients mixed with fillers or binders, such as lactose or starches, lubricants, such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid, or liquid polyethylene glycol with or without stabilizers.

- Pharmaceutical formulations suitable for parenteral administration may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiologically buffered saline. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils, such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate, triglycerides, or liposomes. Non-lipid polycationic amino polymers may also be used for delivery. Optionally, the suspension may also contain suitable stabilizers or agents to increase the solubility of the compounds and allow for the preparation of highly concentrated solutions.

- For topical or nasal administration, penetrants appropriate to the particular barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

The pharmaceutical compositions of the present invention may be manufactured in a manner that is known in the art, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes.

- The pharmaceutical composition may be provided as a salt and can be formed with many acids, including but not limited to, hydrochloric, sulfuric, acetic, lactic, tartaric, malic, and succinic acid. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free base forms. In other cases, the preferred preparation may be a lyophilized powder which may contain any or all of the following: 1 mM to 50 mM histidine, 0.1% to 2% sucrose, and 2% to 7% mannitol, at a pH range of 4.5 to 5.5, that is combined with buffer prior to use.

- After pharmaceutical compositions have been prepared, they can be placed in an appropriate container and labeled for treatment of an indicated condition. For administration of PHSP, such labeling would include amount, frequency, and method of administration.

- Pharmaceutical compositions suitable for use in the invention include compositions wherein the active ingredients are contained in an effective amount to achieve the intended purpose. The determination of an effective dose is well within the capability of those skilled in the art.

For any compound, the therapeutically effective dose can be estimated initially either in cell culture assays, e.g., of neoplastic cells or in animal models such as mice, rats, rabbits, dogs, or pigs. An animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for
5 administration in humans.

A therapeutically effective dose refers to that amount of active ingredient, for example PHSP or fragments thereof, antibodies of PHSP, and agonists, antagonists or inhibitors of PHSP, which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or with experimental animals, such as by
10 calculating the ED_{50} (the dose therapeutically effective in 50% of the population) or LD_{50} (the dose lethal to 50% of the population) statistics. The dose ratio of toxic to therapeutic effects is the therapeutic index, which can be expressed as the LD_{50}/ED_{50} ratio. Pharmaceutical compositions which exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and animal studies are used to formulate a range of dosage for human use. The dosage contained in such
15 compositions is preferably within a range of circulating concentrations that includes the ED_{50} with little or no toxicity. The dosage varies within this range depending upon the dosage form employed, the sensitivity of the patient, and the route of administration.

The exact dosage will be determined by the practitioner, in light of factors related to the subject requiring treatment. Dosage and administration are adjusted to provide sufficient levels of the
20 active moiety or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, the general health of the subject, the age, weight, and gender of the subject, time and frequency of administration, drug combination(s), reaction sensitivities, and response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or biweekly depending on the half-life and clearance rate of the particular
25 formulation.

Normal dosage amounts may vary from about 0.1 μg to 100,000 μg , up to a total dose of about 1 gram, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature and generally available to practitioners in the art. Those skilled in the art will employ different formulations for nucleotides than for proteins or their
30 inhibitors. Similarly, delivery of polynucleotides or polypeptides will be specific to particular cells, conditions, locations, etc.

DIAGNOSTICS

In another embodiment, antibodies which specifically bind PHSP may be used for the diagnosis of disorders characterized by expression of PHSP, or in assays to monitor patients being
35 treated with PHSP or agonists, antagonists, or inhibitors of PHSP. Antibodies useful for diagnostic

purposes may be prepared in the same manner as described above for therapeutics. Diagnostic assays for PHSP include methods which utilize the antibody and a label to detect PHSP in human body fluids or in extracts of cells or tissues. The antibodies may be used with or without modification, and may be labeled by covalent or non-covalent attachment of a reporter molecule. A wide variety of reporter
5 molecules, several of which are described above, are known in the art and may be used.

A variety of protocols for measuring PHSP, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of PHSP expression. Normal or standard values for PHSP expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, preferably human, with antibody to PHSP under conditions suitable
10 for complex formation. The amount of standard complex formation may be quantitated by various methods, preferably by photometric means. Quantities of PHSP expressed in subject, control, and disease samples from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease.

In another embodiment of the invention, the polynucleotides encoding PHSP may be used for
15 diagnostic purposes. The polynucleotides which may be used include oligonucleotide sequences, complementary RNA and DNA molecules, and PNAs. The polynucleotides may be used to detect and quantitate gene expression in biopsied tissues in which expression of PHSP may be correlated with disease. The diagnostic assay may be used to determine absence, presence, and excess expression of PHSP, and to monitor regulation of PHSP levels during therapeutic intervention.

20 In one aspect, hybridization with PCR probes which are capable of detecting polynucleotide sequences, including genomic sequences, encoding PHSP or closely related molecules may be used to identify nucleic acid sequences which encode PHSP. The specificity of the probe, whether it is made from a highly specific region, e.g., the 5' regulatory region, or from a less specific region, e.g., a conserved motif, and the stringency of the hybridization or amplification (maximal, high,
25 intermediate, or low), will determine whether the probe identifies only naturally occurring sequences encoding PHSP, allelic variants, or related sequences.

Probes may also be used for the detection of related sequences, and should preferably have at least 50% sequence identity to any of the PHSP encoding sequences. The hybridization probes of the subject invention may be DNA or RNA and may be derived from the sequence of SEQ ID NO:32-
30 62 or from genomic sequences including promoters, enhancers, and introns of the PHSP gene.

Means for producing specific hybridization probes for DNAs encoding PHSP include the cloning of polynucleotide sequences encoding PHSP or PHSP derivatives into vectors for the production of mRNA probes. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by means of the addition of the appropriate RNA
35 polymerases and the appropriate labeled nucleotides. Hybridization probes may be labeled by a

variety of reporter groups, for example, by radionuclides such as ^{32}P or ^{35}S , or by enzymatic labels, such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems, and the like.

Polynucleotide sequences encoding PHSP may be used for the diagnosis of disorders associated with expression of PHSP. Examples of such disorders include, but are not limited to, a cell
5 proliferative disorder, such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, and cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall
10 bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus; an immune disorder, such as acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyendocrinopathy-
15 candidiasis-ectodermal dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia with lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation,
20 osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, viral, bacterial, fungal, parasitic, protozoal, and helminthic infections, and trauma; and a neuronal disorder, such as akathisia,
25 Alzheimer's disease, amnesia, amyotrophic lateral sclerosis, bipolar disorder, catatonia, dementia, depression, diabetic neuropathy, Down's syndrome, tardive dyskinesia, dystonias, epilepsy, Huntington's disease, peripheral neuropathy, multiple sclerosis, neurofibromatosis, Parkinson's disease, paranoid psychoses, postherpetic neuralgia, schizophrenia, and Tourette's disorder. The polynucleotide sequences encoding PHSP may be used in Southern or northern analysis, dot blot, or
30 other membrane-based technologies; in PCR technologies; in dipstick, pin, and multiformat ELISA-like assays; and in microarrays utilizing fluids or tissues from patients to detect altered PHSP expression. Such qualitative or quantitative methods are well known in the art.

In a particular aspect, the nucleotide sequences encoding PHSP may be useful in assays that detect the presence of associated disorders, particularly those mentioned above. The nucleotide
35 sequences encoding PHSP may be labeled by standard methods and added to a fluid or tissue sample

from a patient under conditions suitable for the formation of hybridization complexes. After a suitable incubation period, the sample is washed and the signal is quantitated and compared with a standard value. If the amount of signal in the patient sample is significantly altered in comparison to a control sample then the presence of altered levels of nucleotide sequences encoding PHSP in the sample
5 indicates the presence of the associated disorder. Such assays may also be used to evaluate the efficacy of a particular therapeutic treatment regimen in animal studies, in clinical trials, or to monitor the treatment of an individual patient.

In order to provide a basis for the diagnosis of a disorder associated with expression of PHSP, a normal or standard profile for expression is established. This may be accomplished by combining
10 body fluids or cell extracts taken from normal subjects, either animal or human, with a sequence, or a fragment thereof, encoding PHSP, under conditions suitable for hybridization or amplification. Standard hybridization may be quantified by comparing the values obtained from normal subjects with values from an experiment in which a known amount of a substantially purified polynucleotide is used. Standard values obtained in this manner may be compared with values obtained from samples
15 from patients who are symptomatic for a disorder. Deviation from standard values is used to establish the presence of a disorder.

Once the presence of a disorder is established and a treatment protocol is initiated, hybridization assays may be repeated on a regular basis to determine if the level of expression in the patient begins to approximate that which is observed in the normal subject. The results obtained from
20 successive assays may be used to show the efficacy of treatment over a period ranging from several days to months.

With respect to cancer, the presence of an abnormal amount of transcript (either under- or overexpressed) in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance
25 of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

Additional diagnostic uses for oligonucleotides designed from the sequences encoding PHSP may involve the use of PCR. These oligomers may be chemically synthesized, generated
30 enzymatically, or produced *in vitro*. Oligomers will preferably contain a fragment of a polynucleotide encoding PHSP, or a fragment of a polynucleotide complementary to the polynucleotide encoding PHSP, and will be employed under optimized conditions for identification of a specific gene or condition. Oligomers may also be employed under less stringent conditions for detection or quantitation of closely related DNA or RNA sequences.

35 Methods which may also be used to quantify the expression of PHSP include radiolabeling

or biotinylating nucleotides, coamplification of a control nucleic acid, and interpolating results from standard curves. (See, e.g., Melby, P.C. et al. (1993) *J. Immunol. Methods* 159:235-244; Duplaa, C. et al. (1993) *Anal. Biochem.* 212:229-236.) The speed of quantitation of multiple samples may be accelerated by running the assay in an ELISA format where the oligomer of interest is presented in various dilutions and a spectrophotometric or colorimetric response gives rapid quantitation.

In further embodiments, oligonucleotides or longer fragments derived from any of the polynucleotide sequences described herein may be used as targets in a microarray. The microarray can be used to monitor the expression level of large numbers of genes simultaneously and to identify genetic variants, mutations, and polymorphisms. This information may be used to determine gene function, to understand the genetic basis of a disorder, to diagnose a disorder, and to develop and monitor the activities of therapeutic agents.

Microarrays may be prepared, used, and analyzed using methods known in the art. (See, e.g., Brennan, T.M. et al. (1995) U.S. Patent No. 5,474,796; Schena, M. et al. (1996) *Proc. Natl. Acad. Sci.* 93:10614-10619; Baldeschweiler et al. (1995) PCT application WO95/251116; Shalon, D. et al. (1995) PCT application WO95/35505; Heller, R.A. et al. (1997) *Proc. Natl. Acad. Sci.* 94:2150-2155; and Heller, M.J. et al. (1997) U.S. Patent No. 5,605,662.)

In another embodiment of the invention, nucleic acid sequences encoding PHSP may be used to generate hybridization probes useful in mapping the naturally occurring genomic sequence. The sequences may be mapped to a particular chromosome, to a specific region of a chromosome, or to artificial chromosome constructions, e.g., human artificial chromosomes (HACs), yeast artificial chromosomes (YACs), bacterial artificial chromosomes (BACs), bacterial P1 constructions, or single chromosome cDNA libraries. (See, e.g., Harrington, J.J. et al. (1997) *Nat Genet.* 15:345-355; Price, C.M. (1993) *Blood Rev.* 7:127-134; and Trask, B.J. (1991) *Trends Genet.* 7:149-154.)

Fluorescent in situ hybridization (FISH) may be correlated with other physical chromosome mapping techniques and genetic map data. (See, e.g., Heinz-Ulrich, et al. (1995) in Meyers, supra, pp. 965-968.) Examples of genetic map data can be found in various scientific journals or at the Online Mendelian Inheritance in Man (OMIM) site. Correlation between the location of the gene encoding PHSP on a physical chromosomal map and a specific disorder, or a predisposition to a specific disorder, may help define the region of DNA associated with that disorder. The nucleotide sequences of the invention may be used to detect differences in gene sequences among normal, carrier, and affected individuals.

In situ hybridization of chromosomal preparations and physical mapping techniques, such as linkage analysis using established chromosomal markers, may be used for extending genetic maps. Often the placement of a gene on the chromosome of another mammalian species, such as mouse, may reveal associated markers even if the number or arm of a particular human chromosome is not known.

New sequences can be assigned to chromosomal arms by physical mapping. This provides valuable information to investigators searching for disease genes using positional cloning or other gene discovery techniques. Once the disease or syndrome has been crudely localized by genetic linkage to a particular genomic region, e.g., ataxia-telangiectasia to 11q22-23, any sequences mapping to that
5 area may represent associated or regulatory genes for further investigation. (See, e.g., Gatti, R.A. et al. (1988) *Nature* 336:577-580.) The nucleotide sequence of the subject invention may also be used to detect differences in the chromosomal location due to translocation, inversion, etc., among normal, carrier, or affected individuals.

In another embodiment of the invention, PHSP, its catalytic or immunogenic fragments, or
10 oligopeptides thereof can be used for screening libraries of compounds in any of a variety of drug screening techniques. The fragment employed in such screening may be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. The formation of binding complexes between PHSP and the agent being tested may be measured.

Another technique for drug screening provides for high throughput screening of compounds
15 having suitable binding affinity to the protein of interest. (See, e.g., Geysen, et al. (1984) PCT application WO84/03564.) In this method, large numbers of different small test compounds are synthesized on a solid substrate. The test compounds are reacted with PHSP, or fragments thereof, and washed. Bound PHSP is then detected by methods well known in the art. Purified PHSP can also be coated directly onto plates for use in the aforementioned drug screening techniques. Alternatively,
20 non-neutralizing antibodies can be used to capture the peptide and immobilize it on a solid support.

In another embodiment, one may use competitive drug screening assays in which neutralizing antibodies capable of binding PHSP specifically compete with a test compound for binding PHSP. In this manner, antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with PHSP.

25 In additional embodiments, the nucleotide sequences which encode PHSP may be used in any molecular biology techniques that have yet to be developed, provided the new techniques rely on properties of nucleotide sequences that are currently known, including, but not limited to, such properties as the triplet genetic code and specific base pair interactions.

Without further elaboration, it is believed that one skilled in the art can, using the preceding
30 description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

The disclosures of all patents, applications, and publications mentioned above and below, in particular U.S. Ser. No. 09/173,482, 09/123,494, 09/152,814, 09/229,005, 60/106,889, 60/109,093,
35 and 60/113,796, are hereby expressly incorporated by reference.

EXAMPLES

I. Construction of cDNA Libraries

RNA was purchased from Clontech or isolated from tissues described in Table 4. Some tissues were homogenized and lysed in guanidinium isothiocyanate, while others were homogenized and lysed in phenol or in a suitable mixture of denaturants, such as TRIZOL (Life Technologies), a monophasic solution of phenol and guanidine isothiocyanate. The resulting lysates were centrifuged over CsCl cushions or extracted with chloroform. RNA was precipitated from the lysates with either isopropanol or sodium acetate and ethanol, or by other routine methods.

Phenol extraction and precipitation of RNA were repeated as necessary to increase RNA purity. In some cases, RNA was treated with DNase. For most libraries, poly(A⁺) RNA was isolated using oligo d(T)-coupled paramagnetic particles (Promega), OLIGOTEX latex particles (QIAGEN, Chatsworth CA), or an OLIGOTEX mRNA purification kit (QIAGEN). Alternatively, RNA was isolated directly from tissue lysates using other RNA isolation kits, e.g., the POLY(A)PURE mRNA purification kit (Ambion, Austin TX).

In some cases, Stratagene was provided with RNA and constructed the corresponding cDNA libraries. Otherwise, cDNA was synthesized and cDNA libraries were constructed with the UNIZAP vector system (Stratagene) or SUPERScript plasmid system (Life Technologies), using the recommended procedures or similar methods known in the art. (See, e.g., Ausubel, 1997, *supra*, units 5.1-6.6). Reverse transcription was initiated using oligo d(T) or random primers. Synthetic oligonucleotide adapters were ligated to double stranded cDNA, and the cDNA was digested with the appropriate restriction enzyme or enzymes. For most libraries, the cDNA was size-selected (300-1000 bp) using SEPHACRYL S1000, SEPHAROSE CL2B, or SEPHAROSE CL4B column chromatography (Amersham Pharmacia Biotech) or preparative agarose gel electrophoresis. cDNAs were ligated into compatible restriction enzyme sites of the polylinker of a suitable plasmid, e.g., PBLUESCRIPT plasmid (Stratagene), pSPORT1 plasmid (Life Technologies), or pINCY (Incyte Pharmaceuticals, Palo Alto CA). Recombinant plasmids were transformed into competent *E. coli* cells including XL1-BLUE, XL1-BLUERF, or SOLR from Stratagene or DH5 α , DH10B, or ELECTROMAX DH10B from Life Technologies.

II. Isolation of cDNA Clones

Plasmids were recovered from host cells by *in vivo* excision, using the UNIZAP vector system (Stratagene) or cell lysis. Plasmids were purified using at least one of the following: a Magic or WIZARD Minipreps DNA purification system (Promega); an AGTC Miniprep purification kit (Edge Biosystems, Gaithersburg MD); and QIAWELL 8 Plasmid, QIAWELL 8 Plus Plasmid, QIAWELL 8 Ultra Plasmid purification systems or the R.E.A.L. PREP 96 plasmid kit from QIAGEN.

Following precipitation, plasmids were resuspended in 0.1 ml of distilled water and stored, with or without lyophilization, at 4 °C.

Alternatively, plasmid DNA was amplified from host cell lysates using direct link PCR in a high-throughput format (Rao, V.B. (1994) Anal. Biochem. 216:1-14). Host cell lysis and thermal
5 cycling steps were carried out in a single reaction mixture. Samples were processed and stored in 384-well plates, and the concentration of amplified plasmid DNA was quantified fluorometrically using PICOGREEN dye (Molecular Probes, Eugene OR) and a Fluoroskan II fluorescence scanner (Labsystems Oy, Helsinki, Finland).

III. Sequencing and Analysis

10 cDNA sequencing reactions were processed using standard methods or high-throughput instrumentation such as the ABI CATALYST 800 (Perkin-Elmer) thermal cyclor or the PTC-200 thermal cyclor (MJ Research) in conjunction with the HYDRA microdispenser (Robbins Scientific) or the MICROLAB 2200 (Hamilton) liquid transfer system. cDNA sequencing reactions were prepared using reagents provided by Amersham Pharmacia Biotech or supplied in ABI sequencing
15 kits such as the ABIPRISM BIGDYE Terminator cycle sequencing ready reaction kit (Perkin-Elmer). Electrophoretic separation of cDNA sequencing reactions and detection of labeled polynucleotides were carried out using the MEGABACE 1000 DNA sequencing system (Molecular Dynamics); the ABI PRISM 373 or 377 sequencing systems (Perkin-Elmer) in conjunction with standard ABI protocols and base calling software; or other sequence analysis systems known in the art. Reading
20 frames within the cDNA sequences were identified using standard methods (reviewed in Ausubel, 1997, supra, unit 7.7). Some of the cDNA sequences were selected for extension using the techniques disclosed in Example V.

The polynucleotide sequences derived from cDNA sequencing were assembled and analyzed using a combination of software programs which utilize algorithms well known to those skilled in the
25 art. Table 5 summarizes the tools, programs, and algorithms used and provides applicable descriptions, references, and threshold parameters. The first column of Table 5 shows the tools, programs, and algorithms used, the second column provides brief descriptions thereof, the third column presents appropriate references, all of which are incorporated by reference herein in their entirety, and the fourth column presents, where applicable, the scores, probability values, and other
30 parameters used to evaluate the strength of a match between two sequences (the higher the score, the greater the homology between two sequences). Sequences were analyzed using MACDNASIS PRO software (Hitachi Software Engineering, South San Francisco CA) and LASERGENE software (DNASTAR).

The polynucleotide sequences were validated by removing vector, linker, and polyA
35 sequences and by masking ambiguous bases, using algorithms and programs based on BLAST,

dynamic programing, and dinucleotide nearest neighbor analysis. The sequences were then queried against a selection of public databases, such as the GenBank primate, rodent, mammalian, vertebrate, and eukaryote databases, and BLOCKS to acquire annotation using programs based on BLAST, FASTA, and BLIMPS. The sequences were assembled into full length polynucleotide sequences using programs based on Phred, Phrap, and Consed, and were screened for open reading frames using programs based on GeneMark, BLAST, and FASTA. The full length polynucleotide sequences were translated to derive the corresponding full length amino acid sequences, and these full length sequences were subsequently analyzed by querying against databases such as the GenBank databases (described above), SwissProt, BLOCKS, PRINTS, Prosite, and Hidden Markov Model (HMM)-based protein family databases such as PFAM. HMM is a probabilistic approach which analyzes consensus primary structures of gene families. (See, e.g., Eddy, S.R. (1996) Curr. Opin. Str. Biol. 6:361-365.)

The programs described above for the assembly and analysis of full length polynucleotide and amino acid sequences were also used to identify polynucleotide sequence fragments from SEQ ID NO:32-62. Fragments from about 20 to about 4000 nucleotides which are useful in hybridization and amplification technologies were described in The Invention section above.

IV. Northern Analysis

Northern analysis is a laboratory technique used to detect the presence of a transcript of a gene and involves the hybridization of a labeled nucleotide sequence to a membrane on which RNAs from a particular cell type or tissue have been bound. (See, e.g., Sambrook, *supra*, ch. 7; Ausubel, 1995, *supra*, ch. 4 and 16.)

Analogous computer techniques applying BLAST were used to search for identical or related molecules in nucleotide databases such as GenBank or LIFESEQ database (Incyte Pharmaceuticals). This analysis is much faster than multiple membrane-based hybridizations. In addition, the sensitivity of the computer search can be modified to determine whether any particular match is categorized as exact or similar. The basis of the search is the product score, which is defined as:

$$\frac{\% \text{ sequence identity} \times \% \text{ maximum BLAST score}}{100}$$

The product score takes into account both the degree of similarity between two sequences and the length of the sequence match. For example, with a product score of 40, the match will be exact within a 1% to 2% error, and, with a product score of 70, the match will be exact. Similar molecules are usually identified by selecting those which show product scores between 15 and 40, although lower scores may identify related molecules.

The results of northern analyses are reported as a percentage distribution of libraries in which the transcript encoding PHSP occurred. Analysis involved the categorization of cDNA libraries by organ/tissue and disease. The organ/tissue categories included cardiovascular, dermatologic,

developmental, endocrine, gastrointestinal, hematopoietic/immune, musculoskeletal, nervous, reproductive, and urologic. The disease/condition categories included cancer, inflammation/trauma, cell proliferation, neurological, and pooled. For each category, the number of libraries expressing the sequence of interest was counted and divided by the total number of libraries across all categories.

- 5 Percentage values of tissue-specific and disease- or condition-specific expression are reported in Table 3.

V. Extension of PHSP Encoding Polynucleotides

The full length nucleic acid sequences of SEQ ID NO:32-62 were produced by extension of an appropriate fragment of the full length molecule using oligonucleotide primers designed from this
10 fragment. One primer was synthesized to initiate 5' extension of the known fragment, and the other primer, to initiate 3' extension of the known fragment. The initial primers were designed using OLIGO 4.06 software (National Biosciences), or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the target sequence at temperatures of about 68°C to about 72°C. Any stretch of nucleotides which would result in
15 hairpin structures and primer-primer dimerizations was avoided.

Selected human cDNA libraries were used to extend the sequence. If more than one extension was necessary or desired, additional or nested sets of primers were designed.

High fidelity amplification was obtained by PCR using methods well known in the art. PCR was performed in 96-well plates using the PTC-200 thermal cycler (MJ Research, Inc.). The reaction
20 mix contained DNA template, 200 nmol of each primer, reaction buffer containing Mg^{2+} , $(NH_4)_2SO_4$, and β -mercaptoethanol, Taq DNA polymerase (Amersham Pharmacia Biotech), ELONGASE enzyme (Life Technologies), and Pfu DNA polymerase (Stratagene), with the following parameters for primer pair PCI A and PCI B: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C. In the
25 alternative, the parameters for primer pair T7 and SK+ were as follows: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 57°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C.

The concentration of DNA in each well was determined by dispensing 100 μ l PICOGREEN quantitation reagent (0.25% (v/v) PICOGREEN; Molecular Probes, Eugene OR) dissolved in 1X TE
30 and 0.5 μ l of undiluted PCR product into each well of an opaque fluorimeter plate (Corning Costar, Acton MA), allowing the DNA to bind to the reagent. The plate was scanned in a Fluoroskan II (Labsystems Oy, Helsinki, Finland) to measure the fluorescence of the sample and to quantify the concentration of DNA. A 5 μ l to 10 μ l aliquot of the reaction mixture was analyzed by electrophoresis on a 1 % agarose mini-gel to determine which reactions were successful in extending
35 the sequence.

The extended nucleotides were desalted and concentrated, transferred to 384-well plates, digested with CviJI cholera virus endonuclease (Molecular Biology Research, Madison WI), and sonicated or sheared prior to religation into pUC 18 vector (Amersham Pharmacia Biotech). For shotgun sequencing, the digested nucleotides were separated on low concentration (0.6 to 0.8%) agarose gels, fragments were excised, and agar digested with Agar ACE (Promega). Extended clones were religated using T4 ligase (New England Biolabs, Beverly MA) into pUC 18 vector (Amersham Pharmacia Biotech), treated with Pfu DNA polymerase (Stratagene) to fill-in restriction site overhangs, and transfected into competent *E. coli* cells. Transformed cells were selected on antibiotic-containing media, individual colonies were picked and cultured overnight at 37°C in 384-well plates in LB/2x carb liquid media.

The cells were lysed, and DNA was amplified by PCR using Taq DNA polymerase (Amersham Pharmacia Biotech) and Pfu DNA polymerase (Stratagene) with the following parameters: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 72°C, 2 min; Step 5: steps 2, 3, and 4 repeated 29 times; Step 6: 72°C, 5 min; Step 7: storage at 4°C. DNA was quantified by PICOGREEN reagent (Molecular Probes) as described above. Samples with low DNA recoveries were reamplified using the same conditions as described above. Samples were diluted with 20% dimethylsulphoxide (1:2, v/v), and sequenced using DYENAMIC energy transfer sequencing primers and the DYENAMIC DIRECT kit (Amersham Pharmacia Biotech) or the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Perkin-Elmer).

In like manner, the nucleotide sequences of SEQ ID NO:32-62 are used to obtain 5' regulatory sequences using the procedure above, oligonucleotides designed for such extension, and an appropriate genomic library.

VI. Labeling and Use of Individual Hybridization Probes

Hybridization probes derived from SEQ ID NO:32-62 are employed to screen cDNAs, genomic DNAs, or mRNAs. Although the labeling of oligonucleotides, consisting of about 20 base pairs, is specifically described, essentially the same procedure is used with larger nucleotide fragments. Oligonucleotides are designed using state-of-the-art software such as OLIGO 4.06 software (National Biosciences) and labeled by combining 50 pmol of each oligomer, 250 µCi of [γ -³²P] adenosine triphosphate (Amersham Pharmacia Biotech), and T4 polynucleotide kinase (DuPont NEN, Boston MA). The labeled oligonucleotides are substantially purified using a SEPHADEX G-25 superfine size exclusion dextran bead column (Amersham Pharmacia Biotech). An aliquot containing 10⁷ counts per minute of the labeled probe is used in a typical membrane-based hybridization analysis of human genomic DNA digested with one of the following endonucleases: Ase I, Bgl II, Eco RI, Pst I, Xba I, or Pvu II (DuPont NEN).

The DNA from each digest is fractionated on a 0.7% agarose gel and transferred to nylon

membranes (Nytran Plus, Schleicher & Schuell, Durham NH). Hybridization is carried out for 16 hours at 40°C. To remove nonspecific signals, blots are sequentially washed at room temperature under increasingly stringent conditions up to 0.1 x saline sodium citrate and 0.5% sodium dodecyl sulfate. Hybridization patterns are compared.

5 VII. Microarrays

A chemical coupling procedure and an ink jet device can be used to synthesize array elements on the surface of a substrate. (See, e.g., Baldeschweiler, *supra*.) An array analogous to a dot or slot blot may also be used to arrange and link elements to the surface of a substrate using thermal, UV, chemical, or mechanical bonding procedures. A typical array may be produced by hand
10 or using available methods and machines and contain any appropriate number of elements. After hybridization, nonhybridized probes are removed and a scanner used to determine the levels and patterns of fluorescence. The degree of complementarity and the relative abundance of each probe which hybridizes to an element on the microarray may be assessed through analysis of the scanned images.

15 Full-length cDNAs, Expressed Sequence Tags (ESTs), or fragments thereof may comprise the elements of the microarray. Fragments suitable for hybridization can be selected using software well known in the art such as LASERGENE software (DNASTAR). Full-length cDNAs, ESTs, or fragments thereof corresponding to one of the nucleotide sequences of the present invention, or selected at random from a cDNA library relevant to the present invention, are arranged on an
20 appropriate substrate, e.g., a glass slide. The cDNA is fixed to the slide using, e.g., UV cross-linking followed by thermal and chemical treatments and subsequent drying. (See, e.g., Schena, M. et al. (1995) *Science* 270:467-470; Shalon, D. et al. (1996) *Genome Res.* 6:639-645.) Fluorescent probes are prepared and used for hybridization to the elements on the substrate. The substrate is analyzed by procedures described above.

25 VIII. Complementary Polynucleotides

Sequences complementary to the PHSP-encoding sequences, or any parts thereof, are used to detect, decrease, or inhibit expression of naturally occurring PHSP. Although use of oligonucleotides comprising from about 15 to 30 base pairs is described, essentially the same procedure is used with smaller or with larger sequence fragments. Appropriate oligonucleotides are
30 designed using OLIGO 4.06 software (National Biosciences) and the coding sequence of PHSP. To inhibit transcription, a complementary oligonucleotide is designed from the most unique 5' sequence and used to prevent promoter binding to the coding sequence. To inhibit translation, a complementary oligonucleotide is designed to prevent ribosomal binding to the PHSP-encoding transcript.

IX. Expression of PHSP

35 Expression and purification of PHSP is achieved using bacterial or virus-based expression

systems. For expression of PHSP in bacteria, cDNA is subcloned into an appropriate vector containing an antibiotic resistance gene and an inducible promoter that directs high levels of cDNA transcription. Examples of such promoters include, but are not limited to, the *trp-lac (tac)* hybrid promoter and the T5 or T7 bacteriophage promoter in conjunction with the *lac* operator regulatory
5 element. Recombinant vectors are transformed into suitable bacterial hosts, e.g., BL21(DE3). Antibiotic resistant bacteria express PHSP upon induction with isopropyl beta-D-thiogalactopyranoside (IPTG). Expression of PHSP in eukaryotic cells is achieved by infecting insect or mammalian cell lines with recombinant Autographica californica nuclear polyhedrosis virus (AcMNPV), commonly known as baculovirus. The nonessential polyhedrin gene of baculovirus is
10 replaced with cDNA encoding PHSP by either homologous recombination or bacterial-mediated transposition involving transfer plasmid intermediates. Viral infectivity is maintained and the strong polyhedrin promoter drives high levels of cDNA transcription. Recombinant baculovirus is used to infect Spodoptera frugiperda (Sf9) insect cells in most cases, or human hepatocytes, in some cases. Infection of the latter requires additional genetic modifications to baculovirus. (See Engelhard, E. K.
15 et al. (1994) Proc. Natl. Acad. Sci. USA 91:3224-3227; Sandig, V. et al. (1996) Hum. Gene Ther. 7:1937-1945.)

In most expression systems, PHSP is synthesized as a fusion protein with, e.g., glutathione S-transferase (GST) or a peptide epitope tag, such as FLAG or 6-His, permitting rapid, single-step, affinity-based purification of recombinant fusion protein from crude cell lysates. GST, a 26-
20 kilodalton enzyme from Schistosoma japonicum, enables the purification of fusion proteins on immobilized glutathione under conditions that maintain protein activity and antigenicity (Amersham Pharmacia Biotech). Following purification, the GST moiety can be proteolytically cleaved from PHSP at specifically engineered sites. FLAG, an 8-amino acid peptide, enables immunoaffinity purification using commercially available monoclonal and polyclonal anti-FLAG antibodies (Eastman
25 Kodak). 6-His, a stretch of six consecutive histidine residues, enables purification on metal-chelate resins (QIAGEN). Methods for protein expression and purification are discussed in Ausubel (1995, supra, ch 10 and 16). Purified PHSP obtained by these methods can be used directly in the following activity assay.

X. Demonstration of PHSP Activity

30 PHSP protein kinase is measured by the phosphorylation of a substrate in the presence of gamma-labeled ^{32}P -ATP. PHSP is incubated with an appropriate substrate and ^{32}P -ATP in a buffered solution. ^{32}P -labeled product is separated from free ^{32}P -ATP by gel electrophoresis or chromatographic procedures, and the incorporated ^{32}P is quantified by phosphorimage analysis or using a scintillation counter. The amount of ^{32}P detected is proportional to the activity of PHSP in
35 this assay. The specific amino acid residue phosphorylated by PHSP may be determined by

phosphoamino acid analysis of the labeled, hydrolyzed protein.

PHSP phosphatase activity is measured by the removal of phosphate from a [^{32}P]-labelled substrate. PHSP is incubated with an appropriate [^{32}P]-labelled substrate in a buffered solution. Reaction products are separated by gel electrophoresis or chromatographic procedures, and the level of ^{32}P associated with the substrate molecule is quantified by phospho-image analysis or scintillation counting. The difference in ^{32}P associated with untreated substrate versus PHSP-treated substrate is a measure of phosphatase activity and is proportional to PHSP activity.

XI. Functional Assays

PHSP function is assessed by expressing the sequences encoding PHSP at physiologically elevated levels in mammalian cell culture systems. cDNA is subcloned into a mammalian expression vector containing a strong promoter that drives high levels of cDNA expression. Vectors of choice include pCMV SPORT (Life Technologies) and pCR3.1 (Invitrogen, Carlsbad CA), both of which contain the cytomegalovirus promoter. 5-10 μg of recombinant vector are transiently transfected into a human cell line, preferably of endothelial or hematopoietic origin, using either liposome formulations or electroporation. 1-2 μg of an additional plasmid containing sequences encoding a marker protein are co-transfected. Expression of a marker protein provides a means to distinguish transfected cells from nontransfected cells and is a reliable predictor of cDNA expression from the recombinant vector. Marker proteins of choice include, e.g., Green Fluorescent Protein (GFP; Clontech), CD64, or a CD64-GFP fusion protein. Flow cytometry (FCM), an automated, laser optics-based technique, is used to identify transfected cells expressing GFP or CD64-GFP and to evaluate properties, for example, their apoptotic state. FCM detects and quantifies the uptake of fluorescent molecules that diagnose events preceding or coincident with cell death. These events include changes in nuclear DNA content as measured by staining of DNA with propidium iodide; changes in cell size and granularity as measured by forward light scatter and 90 degree side light scatter; down-regulation of DNA synthesis as measured by decrease in bromodeoxyuridine uptake; alterations in expression of cell surface and intracellular proteins as measured by reactivity with specific antibodies; and alterations in plasma membrane composition as measured by the binding of fluorescein-conjugated Annexin V protein to the cell surface. Methods in flow cytometry are discussed in Ormerod, M. G. (1994) Flow Cytometry, Oxford, New York NY.

The influence of PHSP on gene expression can be assessed using highly purified populations of cells transfected with sequences encoding PHSP and either CD64 or CD64-GFP. CD64 and CD64-GFP are expressed on the surface of transfected cells and bind to conserved regions of human immunoglobulin G (IgG). Transfected cells are efficiently separated from nontransfected cells using magnetic beads coated with either human IgG or antibody against CD64 (DYNAL, Lake Success NY). mRNA can be purified from the cells using methods well known by those of skill in the art.

Expression of mRNA encoding PHSP and other genes of interest can be analyzed by northern analysis or microarray techniques.

XII. Production of PHSP Specific Antibodies

PHSP substantially purified using polyacrylamide gel electrophoresis (PAGE; see, e.g.,
5 Harrington, M.G. (1990) *Methods Enzymol.* 182:488-495), or other purification techniques, is used to immunize rabbits and to produce antibodies using standard protocols.

Alternatively, the PHSP amino acid sequence is analyzed using LASERGENE software (DNASTAR) to determine regions of high immunogenicity, and a corresponding oligopeptide is synthesized and used to raise antibodies by means known to those of skill in the art. Methods for
10 selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions are well described in the art. (See, e.g., Ausubel, 1995, *supra*, ch. 11.)

Typically, oligopeptides 15 residues in length are synthesized using an ABI 431A peptide synthesizer (Perkin-Elmer) using fmoc-chemistry and coupled to KLH (Sigma-Aldrich, St. Louis MO) by reaction with N-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS) to increase
15 immunogenicity. (See, e.g., Ausubel, 1995, *supra*.) Rabbits are immunized with the oligopeptide-KLH complex in complete Freund's adjuvant. Resulting antisera are tested for anti-peptide activity by, for example, binding the peptide to plastic, blocking with 1% BSA, reacting with rabbit antisera, washing, and reacting with radio-iodinated goat anti-rabbit IgG.

XIII. Purification of Naturally Occurring PHSP Using Specific Antibodies

20 Naturally occurring or recombinant PHSP is substantially purified by immunoaffinity chromatography using antibodies specific for PHSP. An immunoaffinity column is constructed by covalently coupling anti-PHSP antibody to an activated chromatographic resin, such as CNBr-activated SEPHAROSE (Amersham Pharmacia Biotech). After the coupling, the resin is blocked and washed according to the manufacturer's instructions.

25 Media containing PHSP are passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of PHSP (e.g., high ionic strength buffers in the presence of detergent). The column is eluted under conditions that disrupt antibody/PHSP binding (e.g., a buffer of pH 2 to pH 3, or a high concentration of a chaotrope, such as urea or thiocyanate ion), and PHSP is collected.

30 XIV. Identification of Molecules Which Interact with PHSP

PHSP, or biologically active fragments thereof, are labeled with ¹²⁵I Bolton-Hunter reagent. (See, e.g., Bolton et al. (1973) *Biochem. J.* 133:529.) Candidate molecules previously arrayed in the wells of a multi-well plate are incubated with the labeled PHSP, washed, and any wells with labeled PHSP complex are assayed. Data obtained using different concentrations of PHSP are used to
35 calculate values for the number, affinity, and association of PHSP with the candidate molecules.

Various modifications and variations of the described methods and systems of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific
5 embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in molecular biology or related fields are intended to be within the scope of the following claims.

TABLE I

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
1	32	132240	BMARNOT02	132240H1 and 132240R1 (BMARNOT02), 3254142H1 (OVRTUT01), 1453821X14F1 and 1453821F6 (PENITUT01)
2	33	2180116	SININOT01	2180116H1 and 2180116T6 (SININOT01), 3046645H1 (HEAANOT01), 1918183H1 (PROSNOT06), and 1482405F1 (CORPNOT02)
3	34	2197671	SPLNFET02	2197671H1 (SPLNFET02), 666366X22R1 (SCORNOT01), 693783X14 (SYNORAT03), 824265X33F1 (PROSNOT06), 039482R1 and 039482F1 (HUVENOB01), 1453984T6 (PENITUT01), 1663987H1 (BRSTNOT09), and 125901R1 (LUNGNOT01)
4	35	2594943	OVRTUT02	2594943H1 (OVRTUT02), 3617557H1 (EPIPNOT01), 2269005R6 (UTRSNOT02), 1307764F6 (COLNFET02), 1377794F6 (LUNGNOT10), and 1286608H1 (BRAINOT11)
5	36	1513871	PANCTUT01	754239R6 (BRAITUT02), 1513871H1 (PANCTUT01), 2414420F6 (HNT3AZT01), 3291775F6 (BONRFET01), 3821451F6 (BONSTUT01)
6	37	156108	THP1PLB02	156108F1 and 156108H1 (THP1PLB02), 336346R6 (EOSIHET02), 1319528F1 (BLADNOT04), 2375549F6 (ISLTNOT01), SBFA04563F1, SBFA04977F1
7	38	2883243	UTRSTUT05	1342082F6 (COLANTUT03), 1933387T6 (COLNNOT16), 2766460F6 (BRSTNOT12), 2883243H1 (UTRSTUT05), 3524262H1 (ESOGTUN01), 3766487F6 (BRSTNOT24)

TABLE 1 cont.

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
8	39	3173355	UTRSTUT04	1300803F6 and 1300803T6 (BRSTNOT07), 2477542F6 (SMCANOT01), 2477542T6 (SMCANOT01), 2875968H1 (THYRNOT10), 3173355F6 and 3173355H1 (UTRSTUT04), 3290825H1 (BONRFET01), 5192561H1 (OVARDIT06)
9	40	5116906	SMCBUNT01	267517F1 (HNT2NOT01), 263823R1 (HNT2AGT01), 5116906H1 (SMCBUNT01)
10	41	940589	ADRENOT03	029801R6 (SPLNFET01), 940589H1 (ADRENOT03), 1737403T6 (COLNNOT22), 1805477F6 and 1805477T6 (SINTNOT13), 2447613H1 (THP1NOT03), 3408563H1 (PROSTUS08), 3519506H1 (LUNGNON03), 3637343T6 (LUNGNOT30)
11	42	304421	TESTNOT04	304421H1, 304421X318B2, and 304421X323B2 (TESTNOT04), 2639579F6 (BONTNOT01), 2951859H1 (KIDNFET01)
12	43	1213802	BRSTTUT01	894574R1 (BRSTNOT05), 1213802H1 (BRSTTUT01), 1233414F1 and 1234238H1 (LUNGFET03), 1255782F2 and 1255782T1 (MENITUT03), 1455429F1 (COLNFET02), 1576102T1 (LNODNOT03), 2189267F6 (PROSNOT26), 2748179F6 (LUNGUTUT11), 2831667H1 (TLYMNOT03), 3031229H1 (TLYMNOT05), 3054893H1 (LNODNOT08), 3797030F6 (SPLNNOT12), 3880154H1 (SPLNNOT11), 4852525H1 (TESTNOT10), 5514137H1 (BRADDIR01), 5518378H1 (LIVRDIR01)
13	44	1378134	LUNGNOT10	1378134H1 and 1378134X11 (LUNGNOT10), 2205185F6 (SPLNFET02), 4959694H1 (TLYMNOT05), SAMA00107F1, SAMA00160F1, SAMA00020F1

TABLE 1 cont.

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
14	45	1490070	UCMCL5T01	432218H1 (BRAVUNT02), 1490070H1 (UCMCL5T01), 1535394F1 (SPLNNOT04), 1616509F6 and 1616509T6 (BRAITUT12), 2490845H1 (EOSITXT01), 2723789F6 (LUNGTTUT10), SACA00263F1
15	46	1997814	BRSTTUT03	855350R1 (NGANNOT01), 875417R1 (LUNGAST01), 895096R1 (BRSTNOT05), 1271348F1 (TESTTUT02), 1331289F6 (PANCNOT07), 1359243F1 (LUNGNOT12), 1540824T1 (SINTTUT01), 1839828H1 (EOSITXT01), 1997814H1 (BRSTTUT03), 2170638F6 (ENDCNOT03), 3751363F6 (UTRSNOT18)
16	47	2299715	BRSTNOT05	637354R6 and 637354T6 (NEUTGMT01), 1852144F6 (LUNGFET03), 2172576F6 (ENDCNOT03), 2232449F6 (PROSNOT16), 2299715H1 (BRSTNOT05), 2509737X325D2 (CONUTUT01), 2606210F6 (LUNGTTUT07), 2692024F6 (LUNGNOT23), 2805893F6 (BLADTTUT08), 2986160H1 (CARGDIT01), 3085382H1 (HEAONOT03), 3136101F6 and 3136587H1 (SMCCNOT01), 4249977H1 (BRADDIRO1)
17	48	209854	SPLNNOT02	209854H1 and 209854T6 (SPLNNOT02), 3152165R6 and 3152165T6 (ADRENON04)
18	49	1384286	BRAITUT08	676123R6 and 676123T6 (CRBLNOT01), 989218X11 and 989218X12 (LVENNOT03), 1384286H1 (BRAITUT08), 3099868H1 (PROSBPT03), 4693167H1 (BRAENOT02)
19	50	1512656	PANCTUT01	322847X5 (EOSIHET02), 1253795T6 (LUNGFET03), 1512656H1 (PANCUTUT01), 1561686X303D1 (SPLNNOT04), 2212305H1 (SINTFET03), 2697679H1 (UTRSNOT12), 3205172H1 (PENCNOT03), 5313318H1 (KIDETXS02)

TABLE 1 cont.

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
20	51	2098635	BRAITUT02	1268848T1, 1268848X301F1, and 2157157H1 (BRAINTOT09), 2098635H1 and 2098635R6 (BRAITUT02), 2198819F6, 2198819X301D4, 2198819X303D1, 2198819X309B2, and 2198819X309D4 (SPLNFET02), 2784975H2 (BRSTNOT13), 3320340H1 (PROSBPT03)
21	52	2446646	THP1NOT03	000297R6 and 000297X61 (U937NOT01), 2446646H1 (THP1NOT03), 2557274F6 (THYMNOT03)
22	53	2764911	BRSTNOT12	678618T6 and 678618X14 (UTRSNOT02), 2304126R6 (BRSTNOT05), 2764911H1 (BRSTNOT12), 2834475F6 (TLYMNOT03), 2915803F6 (THYMFET03), 3035012F6 (TLYMNOT05), SAFC00027F1, SAFC00254F1, SAFC02376F1, SAFC01609F1
23	54	3013946	MUSCNOT07	673753H1 (CRBLNOT01), 989218X11 and 989218X14 (LVENNOT03), 2821720F6 (ADRETUT06), 3013946F6, 3013946H1, and 3013946T6 (MUSCNOT07), 4693167H1 (BRAENOT02)
24	55	067967	HUVESTB01	067967X92, 067966R1, and 067967H1 (HUVESTB01), SAIA02074F1, SAIA03254F1, SAIA03603F1, and SAIA02259F1
25	56	346275	THYMNOT02	346275H1 (THYMNOT02), 609792X12 (COLNNOT01), SAGA03543F1, SAGA02528F1, and SAGA00285F1
26	57	283746	CARDNOT01	283746H1 and 283746X10 (CARDNOT01), 4903108H1 (TLYMNOT08), 557918X15 (MPHGLPT02), and 2379045F6 (ISLTNOT01)
27	58	2696537	UTRSNOT12	2696537H1 (UTRSNOT12), 3173337F6 (UTRSTUT04), 082658X100 (HUVESTB01), and 603219T6 (BRSTTUT01)

TABLE 1 cont.

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
28	59	551178	BEPINOT01	551178H1 (BEPINOT01), 861522R1 (BRAITUT03), 965838R1 (BRSTNOT05), 1574007F1 and 1574007T1 (LNODNOT03), 1830083T6 and 1831194T6 (THP1AZT01), 3098496H1 (CERVNOT03), 3293481H1 (TLYJINT01)
29	60	619292	PGANNOT01	613165F1 (COLNTUT02), 619292H1 and 619292X13 (PGANNOT01)
30	61	2054049	BEPINOT01	1736355F6 (COLNNOT22), 2054049H1 (BEPINOT01), 2379092T6 (ISLTNOT01), 3127284T3 (LUNGUT12), 3136377F6 (SMCCNOT01), SBMA00545F1, SBMA00827F1, SBMA02930F1, SBMA02853F1
31	62	2843910	DRGLNOT01	036294X71 (HUVENOB01), 066017X102, 068399R1, and 068399X3 (HUVESTB01), 1527276H1 (UCMCL5T01), 1846570T6 (COLNNOT09), 2843910H1 (DRGLNOT01)

TABLE 2

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous sequences	Analytical Methods
1	300	S3 S15 S19 S20 S24 T98 S125 S231 T238 S257 S282 S12 S41 S70 T120 T143 S146 T242	N85 N88 N96	Protein kinase motifs: G161-P256 catalytic tk domain IX: V180-E202	Protein kinase	BLAST PFAM PRINTS
2	147	S85 T38 S90		Calcium-binding repeat motifs: G28-L115	PKC- potentiated inhibitory protein of PP1 (CPI17)	BLAST PRINTS BLOCKS
3	431	T178 S282 T25 S34 S75 S106 S194 S198 T208 T264 S299 S303 S304 S308 T328 S345 S388 T46 S137 S260	N44 N242	PTK signatures: A18-Y283 ATP-binding site: I30-K53, E127-G164 Y196-H219 PK catalytic subdomains: M99-E112, Y134-L152 G181-I191, Y243- A265	Ste20-like protein kinase	BLOCKS PRINTS PROFILES SCAN BLAST
4	218	S108 S68 S90 T133 T170 S172 T34 T123 T207		Phosphofructokinase domains: I47, V177-Q195 L148-Y164		PRINTS

TABLE 2 cont.

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous sequences	Analytical Methods
5	474	S14 S89 S98 S132 S472 T22 S26 S62 S66 T204 T320 T345 T359 S427 S443 S94 S128 T211 T336 S443 Y155		Protein kinase family signature: Y144-F425	serine /threonine protein kinase	MOTIFS PFAM BLOCKS PRINTS ProfileScan BLAST
6	540	S102 S183 S267 T296 T301 S442 S34 S58 S180 S207 S224 T360 S374 S401 S428 S478 T484 Y23	N100 N391 N457 N537	Protein kinase family signature: L18-L287	serine /threonine protein kinase	MOTIFS PFAM BLOCKS PRINTS PROFILESCAN BLAST
7	454	S57 S69 S130 T203 T212 S338 S420 S91 T101 T220 S271 S295 T315 S359 S381 Y197	N55 N140 N218 N403 N437 N441	SH2 domain: W63-Y138, W354-Y428 PI 3 kinase P85 regulator: K153-G176, A216- N257, R287-N332	phosphatidyl- inositol 3- kinase	PFAM BLOCKS PRINTS BLAST
8	502	S246 T498 T21 S65 S76 T193 T203 S275 S312 S355 T484 S106 T222 S323 T498 Y347	N302 N414	Signal peptide: M1-T21 SH2 domain: V70-E80 ER targeting signal: K499-L502	tyrosine kinase	SigPept BLOCKS MOTIFS BLAST

TABLE 2 (cont.)

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous sequences	Analytical Methods
9	281	T66 T140 T141 T182 S210	N117 N139	Signal peptide: M1-I76	calcium /calmodulin- dependent protein kinase	PFAM BLAST
10	510	T297 S323 S358 S51 T312 S323 T325 S329 T377 T390 T483 S24 S152 T201 S210 S247 T292 T406 T407	N185 N349 N381 N405	Protein kinase family signature: R52-V261	Serine /threonine protein kinase	PFAM BLOCKS PRINTS MOTIFS BLAST
11	248	S5 S20 S36 T210 T245	N208	Tyrosine specific phosphatase active site: F166-A220 Dual specificity phosphatase: H95-R240	Tyrosine phosphatase or Dual specificity phosphatase	BLAST, MOTIFS BLOCKS, PRINTS PROFILES SCAN PFAM

TABLE 2 cont.

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous sequences	Analytical Methods
12	810	S62 S290 T429 S758 T17 T104 S108 T216 S279 T316 S330 T360 S386 T405 S425 S465 T473 S497 T547 T561 T715 S733 S738 S768 S196 S222 S229 S267 T281 T321 T347 S370 T400 T512 S534 T609 S617 S663 S751 T754 T762 Y67	N33		Protein kinase	BLAST, MOTIFS
13	549	S6 T502 T21 T116 S125 S320 T417 S46 S87 T240 S390 S397 S405 S430 S497	N238	ATP/GTP-binding site (p-loop): G58-T65 Protein kinase signature: I176-K199 I292-L304 Y347-L370 F456-L483	Dual specificity tyrosine /serine protein kinase	BLAST, MOTIFS BLOCKS, PRINTS PFAM
14	416	S312 T20 T97 S104 S183 T185 T211 T274 S381 S411 S72 S79 S140 S318 Y53		SH3 domain: A366-D384 N402-E414	PEST phosphatase interacting protein	BLAST, MOTIFS BLOCKS, PRINTS PFAM

TABLE 2 cont.

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous sequences	Analytical Methods
15	425	T34 S233 S234 S25 S107 T144 T198 T250 S251 S258 S282 S300 S324 S345 T390 T51 T133 S365 S383 Y71	N23 N176 N362		SH3 binding protein	BLAST, MOTIFS
16	1135	S77 T187 S259 S554 S815 S9 S17 T59 S112 T124 T222 S264 T319 S324 S326 S550 T572 S625 S681 S682 T688 T689 S706 S720 T931 S958 S978 S999 S255 T309 T351 T543 S550 S624 S632 S726 T811 S898 S1012 S1113 Y321 Y323 Y467	N33 N570 N718 N1067	Protein kinase signature: V31-K54 V149-L161 W129-V182 Tyrosine kinase catalytic site: G190-I200 S214-M236 NIK1-like kinase domain: Y836-R1115	NIK kinase	BLAST, MOTIFS PROFILES BLOCKS, PRINTS PFAM
17	228	T163 S60 T78 T68 S88 S147	N19 N100 N114		Interferon- induced PK regulator (P52rIPK)	BLAST

TABLE 2 cont.

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous sequences	Analytical Methods
18	503	S51 T262 T36 S79 T94 S109 T361 T362 T403 S472 T47 S334 S343 Y17	N313 N333 N360	Protein kinase signature: I20-K43 V132-L144 V195-E217 Protein kinase domain: Y14-V272	calcium /calmodulin- dependent protein kinase II, beta 3 isoform	BLAST, BLOCKS, PRINTS, MOTIFS, PFAM, PROFILES SCAN
19	433	S12 S77 S124 S131 S255 S290 T327 S365 S402 T70 Y88			Choline kinase isolog 384D8_3	BLAST, MOTIFS
20	527	S417 S154 S199 T367 S453 T120 S178 S413 T447 S473	N470	Protein kinase signature: I144-K167 I260-V172 ATP-binding site: Q247-G284 Y318-F341 Protein kinase domain: I138-L427	MAP-related protein kinase	BLAST, BLOCKS MOTIFS, PFAM, PROFILES SCAN

TABLE 2 cont.

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous sequences	Analytical Methods
21	322	S19 S122 T198 T200 T236 S251 T260 S264 T301 S14 S52 T181 T225	N196 N249	Protein kinase signature: L163-I175 ATP-binding site: M150-V187 I224-H247 Protein kinase domain: S32-E316	Protein tyrosine kinase	BLAST, BLOCKS, PRINTS, MOTIFS, PFAM, PROFILES CAN
22	802	S70 T87 S750 T14 T98 S144 T150 S230 S263 T353 T465 T470 S517 S633 T751 S758 T27 T74 T100 T207 S268 S368 S458	N36 N655	Protein kinase signature: L55-K81, L432-K455 ATP-binding site: E160-G197, H232-F255 PTK catalytic domain: H534-F552, C603-H625 Protein kinase domains: F49-F318, L427-L687 Protein kinase C domain: Q319-I382	Ribosomal S6 protein kinase	BLAST, BLOCKS, PRINTS, MOTIFS, PFAM, PROFILES CAN
23	641	S51 T262 S398 S436 S479 T36 S79 T94 S109 T375 T376 T541 S610 T47 S315 S333 S342 S393 S422 S431 S465 S474 S508 Y17	N313 N332 N374	Protein kinase signature: I20-K43 V132-L144 ATP-binding site: Q119-A156 Y191-F214 Protein kinase domain: Y14-V272	Ca2+ /calmodulin dependent protein kinase	BLAST, BLOCKS, PRINTS, MOTIFS, PFAM, PROFILES CAN

TABLE 2 cont.

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous sequences	Analytical Methods
24	588	S106 T155 S359 T388 T456 T531 T4, S58 S108 T126 S132 T279 S350 S436 S469 S508 S537 Y32	N63 N130 N574	Protein kinase catalytic domain: Y209-S445, F495-I522 ATP-binding site: I215-K238 STK core catalytic motif: I331-L343	Protein kinase Dyrk2	MOTIFS PFAM BLOCKS PRINTS BLAST
25	389	S31 T301 S56 S96 S134 T149 S186 S201 S283 S358 S375 Y148 Y165	N257 N343 N364	Protein kinase catalytic domain: E73-I311 STK core catalytic motif: I172-Y184 PTK core domain: D152-D208	Cam-like protein kinase	BLAST PFAM MOTIFS BLOCKS PRINTS PROFILES SCAN
26	343	S68 S81 S137 S184 T219 S276 S297 T29 T125 Y86 Y211	N332	EF hand calcium-binding signature: D176-L188	protein phosphatase 2A (PR72)	BLAST MOTIFS BLOCKS
27	184	S36 T105 S40 S70 T117 Y50	N62	Tyrosine phosphatase active site domain: L63-V118	MAP kinase phosphatase (X17C)	BLAST PROFILES SCAN BLOCKS PRINTS MOTIFS

TABLE 2 cont.

Polypeptide SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence	Homologous sequences	Analytical Methods
28	367	S10 S21 S44 S103 T116 T267 T309 S191 S213 S218 S256 T305 S352 Y159 Y344	N16 N17		protein phosphatase 2A, A-subunit	BLAST
29	118	S34 S84	N43	Signal peptide: M1-A27 PDZ domain: H8-S73	tyrosine phosphatase	SPScan PFAM BLAST
30	356	S9 S94 T209 T220 S259 S337 S5 S26 S75 S121 T154 S282 S332 S339 Y15 Y84	N333	tyrosine-specific protein phosphatase active site: I108-K164	tyrosine phosphatase (myotubularin)	PROFILES MOTIFS BLOCKS PRINTS BLAST
31	453	S38 S73 S119 S131 S193 S200 T236 S293 S341 T379 T124 S173 T214 S252 T256 S282 S302 S313 S391 S397	N43 N67 N357	protein phosphatase 2A p55 subunit: P10-K451	protein phosphatase 2A p55 regulatory subunit, alpha isoform	PFAM MOTIFS BLOCKS PRINTS BLAST

TABLE 3

Nucleotide SEQ ID NO:	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
32	Hematopoietic/Immune (0.333) Reproductive (0.333)	Cell proliferation (0.500) Inflammation (0.333)	PBLUESCRIPT
33	Nervous (0.216) Reproductive (0.235) Cardiovascular (0.118)	Cell proliferation (0.530) Inflammation (0.352)	pINCY
34	Reproductive (0.293) Gastrointestinal (0.192)	Cell proliferation (0.641) Inflammation (0.335)	pINCY
35	Reproductive (0.284) Nervous (0.210) Cardiovascular (0.1213)	Cell proliferation (0.729) Inflammation (0.272)	pINCY
36	Nervous (0.529) Developmental (0.118) Gastrointestinal (0.118)	Cell proliferation (0.588) Neurological (0.118) Inflammation (0.118)	pINCY
37	Hematopoietic/Immune (0.268) Reproductive (0.244) Nervous (0.122)	Inflammation (0.488) Cell Proliferative (0.415)	PBLUESCRIPT
38	Reproductive (0.400) Hematopoietic/Immune (0.160) Nervous (0.160)	Cell proliferation (0.600) Inflammation (0.320)	pINCY
39	Cardiovascular (0.312) Reproductive (0.312) Developmental (0.188)	Cell proliferation (0.938) Inflammation (0.125)	pINCY
40	Nervous (0.400) Gastrointestinal (0.267) Developmental (0.133)	Cell proliferation (0.733) Neurological (0.133) Inflammation (0.133)	pINCY
41	Gastrointestinal (0.267) Nervous (0.233) Reproductive (0.167)	Inflammation (0.533) Cell proliferation (0.534)	pSPORT1

Table 3 cont.

Nucleotide SEQ ID NO:	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
42	Musculoskeletal (0.500) Developmental (0.167) Gastrointestinal (0.167)	Cancer (0.834) Inflammation (0.167)	PBLUESCRIPT
43	Reproductive (0.240) Nervous (0.151) Gastrointestinal (0.135)	Cell proliferation (0.536) Inflammation (0.417)	pSPORT1
44	Hematopoietic/Immune (0.278) Nervous (0.222) Dermatologic (0.111)	Cell proliferation (0.444) Inflammation (0.389)	pINCY
45	Hematopoietic/Immune (0.500) Gastrointestinal (0.125) Nervous (0.125)	Inflammation (0.500) Cell proliferative (0.500)	PBLUESCRIPT
46	Nervous (0.220) Reproductive (0.213) Hematopoietic/Immune (0.140)	Cell proliferation (0.573) Inflammation (0.380)	pSPORT1
47	Hematopoietic/Immune (0.190) Gastrointestinal (0.165) Nervous (0.139)	Cell proliferation (0.582) Inflammation (0.354)	pSPORT1

Table 3 cont.

Nucleotide SEQ ID NO:	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
48	Nervous (0.333) Reproductive (0.333) Hematopoietic/Immune (0.111)	Cancer (0.444) Inflammation (0.222) Neurological (0.111)	PBLUESCRIPT
49	Nervous (0.724) Cardiovascular (0.103)	Inflammation (0.276) Cancer (0.241) Neurological (0.172)	pINCY
50	Reproductive (0.235) Hematopoietic/Immune (0.188) Gastrointestinal (0.129)	Cancer (0.447) Inflammation (0.282) Fetal (0.153)	pINCY
51	Nervous (0.368) Developmental (0.158) Gastrointestinal (0.105)	Cancer (0.368) Fetal (0.211) Inflammation (0.105)	pSPORT1
52	Cardiovascular (0.312) Hematopoietic/Immune (0.312) Reproductive (0.158)	Fetal (0.688) Cancer (0.421) Inflammation (0.125)	pINCY
53	Reproductive (0.412) Nervous (0.235) Developmental (0.118)	Cancer (0.471) Fetal (0.235) Inflammation (0.235)	pINCY
54	Nervous (0.714) Cardiovascular (0.107)	Cancer (0.250) Inflammation (0.250) Neurological (0.179)	pINCY

Table 3 cont.

Nucleotide SEQ ID NO:	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	PBLUESCRIPT
55	Reproductive (0.533) Nervous (0.133)	Cell proliferation (0.601) Inflammation (0.270)	PBLUESCRIPT
56	Hematopoietic/Immune (0.278) Nervous (0.222) Reproductive (0.154)	Cell proliferation (0.388) Inflammation (0.333) Neurological (0.111)	PBLUESCRIPT
57	Hematopoietic/Immune (0.211) Cardiovascular (0.193) Nervous (0.175)	Cell proliferation (0.474) Inflammation (0.491)	PBLUESCRIPT
58	Reproductive (0.286) Cardiovascular (0.229) Musculoskeletal (0.143)	Cell proliferation (0.715) Inflammation (0.200)	PINCY
59	Reproductive (0.253) Gastrointestinal (0.211) Nervous (0.147)	Cancer and Cell proliferation (0.684) Inflammation and Immune Response (0.242)	PSPORT1
60	Nervous (0.667) Reproductive (0.333)	Cancer (1.000)	PSPORT1
61	Reproductive (0.357) Cardiovascular (0.179) Nervous (0.125)	Cancer and Cell proliferation (0.642) Inflammation and Immune Response (0.232)	PSPORT1
62	Nervous (0.228) Reproductive (0.175) Cardiovascular (0.158) Hematopoietic/Immune (0.158)	Cancer (0.368) Inflammation and Immune Response (0.263) Fetal (0.211)	PINCY

TABLE 4

Polynucleotide SEQ ID NO:	Library	Library Comment
32	BMARNOT02	Library was constructed using RNA isolated from the bone marrow of 24 male and female Caucasian donors, 16 to 70 years old.
33	SININOT01	Library was constructed using RNA isolated from ileum tissue removed from the small intestine of a 4-year-old Caucasian female, who died from a closed head injury. Patient history included jaundice as a baby. Previous surgeries included a double hernia repair
34	SPLNFET02	Library was constructed using RNA isolated from spleen tissue removed from a Caucasian male fetus, who died at 23 weeks' gestation from premature birth. Family history included diabetes.
35	OVARTUT02	Library was constructed using RNA isolated from ovarian tumor tissue removed from a 51-year-old Caucasian female during an exploratory laparotomy, total abdominal hysterectomy, salpingo-oophorectomy, and an incidental appendectomy. Pathology indicated mucinous cystadenoma presenting as a multiloculated neoplasm involving the entire left ovary. The right ovary contained a follicular cyst and a hemorrhagic corpus luteum. The uterus showed proliferative endometrium and a single intramural leiomyoma. The peritoneal biopsy indicated benign glandular inclusions consistent with endosalpingiosis. The patient presented with abnormal weight gain and ascites. Patient history included depressive disorder, joint pain, allergies, alcohol use, and a normal delivery. Family history included atherosclerotic coronary artery disease, benign hypertension, breast cancer and uterine cancer.

TABLE 4 cont.

Polynucleotide SEQ ID NO:	Library	Library Comment
36	PANCTUT01	Library was constructed using RNA isolated from pancreatic tumor tissue removed from a 65-year-old Caucasian female during radical subtotal pancreatectomy. Pathology indicated an invasive grade 2 adenocarcinoma. Patient history included type II diabetes, osteoarthritis, cardiovascular disease, and benign neoplasm in the large bowel. Previous surgeries included a total splenectomy, cholecystectomy, and abdominal hysterectomy. Family history included cardiovascular disease, type II diabetes, and stomach cancer.
37	SMCBUNT01	Library was constructed using RNA isolated from bronchial smooth muscle cell tissue removed from a 21-year-old Caucasian male.
38	UTRSTUT05	Library was constructed using RNA isolated from uterine tumor tissue removed from a 41-year-old Caucasian female during a vaginal hysterectomy with dilation and curettage. Pathology indicated uterine leiomyoma. The endometrium was secretory and contained fragments of endometrial polyps. Benign endo- and ectocervical mucosa were identified in the endocervix. Patient history included a ventral hernia and a benign ovarian neoplasm.
39	UTRSTUT04	Library was constructed using RNA isolated from uterine tumor tissue removed from a 34-year-old Caucasian female during a hysteroscopy and an exploratory laparotomy with dilation and curettage. Pathology indicated an endometrial polyp, subserosal leiomyoma, and fragments of leiomyoma. Family history included hyperlipidemia, depressive disorder, benign hypertension, cerebrovascular disease, arteriosclerotic cardiovascular disease, and type II diabetes.

TABLE 4 cont.

Polynucleotide SEQ ID NO:	Library	Library Comment
40	SMCBUNT01	library was constructed using RNA isolated from bronchial smooth muscle cell tissue removed from a 21-year-old Caucasian male.
41	ADRENOT03	library was constructed using RNA isolated from the adrenal tissue of a 17-year-old Caucasian male, who died from cerebral anoxia.
42	TESTNOT04	library was constructed using RNA isolated from testicular tissue removed from a 37-year-old Caucasian male who died from liver disease. Patient history included cirrhosis, jaundice, and liver failure.
43	BRSTTUT01	library was constructed using RNA isolated from breast tumor tissue removed from a 55-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology indicated invasive grade 4 mammary adenocarcinoma of mixed lobular and ductal type, extensively involving the left breast. The tumor was identified in the deep dermis near the lactiferous ducts with extracapsular extension. Seven mid and low and five high axillary lymph nodes were positive for tumor. Proliferative fibrocystic changes were characterized by apocrine metaplasia, sclerosing adenosis, cyst formation, and ductal hyperplasia without atypia. Patient history included atrial tachycardia, blood in the stool, and a benign breast neoplasm. Family history included benign hypertension, atherosclerotic coronary artery disease, cerebrovascular disease, and depressive disorder.
44	LUNGNOT10	library was constructed using RNA isolated from the lung tissue of a Caucasian male fetus who died at 23 weeks' gestation.
45	UCMCL5T01	library was constructed using RNA isolated from mononuclear cells obtained from the umbilical cord blood of 12 individuals. The cells were cultured for 12 days with IL-5 before RNA was isolated from the pooled lysates.

TABLE 4 cont.

Polynucleotide SEQ ID NO:	Library	Library Comment
46	BRSTTUT03	Library was constructed using RNA isolated from breast tumor tissue removed from a 58-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology indicated multicentric invasive grade 4 lobular carcinoma. The mass was identified in the upper outer quadrant, and three separate nodules were found in the lower outer quadrant of the left breast. Patient history included skin cancer, rheumatic heart disease, osteoarthritis, and tuberculosis. Family history included cerebrovascular disease, coronary artery aneurysm, breast cancer, prostate cancer, atherosclerotic coronary artery disease, and type I diabetes.
47	BRSTNOT05	Library was constructed using RNA isolated from breast tissue removed from a 58-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology for the associated tumor tissue indicated multicentric invasive grade 4 lobular carcinoma. Patient history included skin cancer, rheumatic heart disease, osteoarthritis, and tuberculosis. Family history included cerebrovascular and cardiovascular disease, breast and prostate cancer, and type I diabetes.

TABLE 4 cont.

Polynucleotide SEQ ID NO:	Library	Library Comment
48	SPLNNOT02	The library was constructed using RNA isolated from the spleen tissue of a 29-year-old Caucasian male, who died from head trauma. Serologies were positive for cytomegalovirus (CMV). Patient history included alcohol, marijuana, and tobacco use.
49	BRAITUT08	The library was constructed using RNA isolated from brain tumor tissue removed from the left frontal lobe of a 47-year-old Caucasian male during excision of cerebral meningeal tissue. Pathology indicated grade 4 fibrillary astrocytoma with focal tumoral radionecrosis. Patient history included cerebrovascular disease, deficiency anemia, hyperlipidemia, epilepsy, and tobacco use. Family history included cerebrovascular disease and a malignant prostate neoplasm.
50	PANCTUT01	The library was constructed using RNA isolated from pancreatic tumor tissue removed from a 65-year-old Caucasian female during radical subtotal pancreatectomy. Pathology indicated an invasive grade 2 adenocarcinoma. Patient history included type II diabetes, osteoarthritis, cardiovascular disease, benign neoplasm in the large bowel, and a cataract. Previous surgeries included a total splenectomy, cholecystectomy, and abdominal hysterectomy. Family history included cardiovascular disease, type II diabetes, and stomach cancer.
51	BRAITUT02	The library was constructed using RNA isolated from brain tumor tissue removed from the frontal lobe of a 58-year-old Caucasian male during excision of a cerebral meningeal lesion. Pathology indicated a grade 2 metastatic hypernephroma. Patient history included a grade 2 renal cell carcinoma, insomnia, and chronic airway obstruction. Family history included a malignant neoplasm of the kidney.

TABLE 4 cont.

Polynucleotide SEQ ID NO:	Library	Library Comment
52	THP1NOT03	The library was constructed using RNA isolated from untreated THP-1 cells. THP-1 (ATCC TIB 202) is a human promonocyte line derived from the peripheral blood of a 1-year-old Caucasian male with acute monocytic leukemia (ref: Int. J. Cancer (1980) 26:171).
53	BRSTNOT12	The library was constructed using RNA isolated from diseased breast tissue removed from a 32-year-old Caucasian female during a bilateral reduction mammoplasty. Pathology indicated nonproliferative fibrocystic disease. Family history included cardiovascular disease.
54	MUSCNOT07	The library was constructed using RNA isolated from muscle tissue removed from the forearm of a 38-year-old Caucasian female during a soft tissue excision. Pathology for the associated tumor tissue indicated intramuscular hemangioma. Family history included breast cancer, benign hypertension, cerebrovascular disease, colon cancer, and type II diabetes.
55	HUVESTB01	Library was constructed using RNA isolated from shear-stressed HUV-EC-C (ATCC CRL 1730) cells. HUV-EC-C is an endothelial cell line derived from the vein of a normal human umbilical cord (ref:PNAS 81:6413).
56	THYMNOT02	Library was constructed using polyA RNA isolated from thymus tissue removed from a 3-year-old Caucasian male, who died from drowning.
57	CARDNOT01	Library was constructed using RNA isolated from the cardiac muscle of a 65-year-old Caucasian male, who died from a self-inflicted gunshot wound.

TABLE 4 cont.

Polynucleotide SEQ ID NO:	Library	Library Comment
58	UTRSNOT12	Library was constructed using RNA isolated from uterine myometrial tissue removed from a 41-year-old Caucasian female during a vaginal hysterectomy with a dilatation and curettage. The endometrium was secretory and contained fragments of endometrial polyps. Benign endo- and ectocervical mucosa were identified in the endocervix. Pathology for the associated tumor tissue indicated uterine leiomyoma. The patient presented with an unspecified menstrual disorder. Patient history included ventral hernia, normal delivery, a benign ovarian neoplasm, and tobacco abuse. Previous surgeries included a bilateral destruction of fallopian tubes, removal of a solitary ovary, and an exploratory laparotomy.
59	BEPINOT01	Library was constructed using RNA isolated from a bronchial epithelium primary cell line derived from a 54-year-old Caucasian male.
60	PGANNOT01	Library was constructed using RNA isolated from paraganglionic tumor tissue removed from the intra-abdominal region of a 46-year-old Caucasian male during exploratory laparotomy. Pathology indicated a benign paraganglioma and association with a grade 2 renal cell carcinoma, clear cell type.
61	BEPINOT01	Library was constructed using RNA isolated from a bronchial epithelium primary cell line derived from a 54-year-old Caucasian male.
62	DRGLNOT01	Library was constructed using RNA isolated from dorsal root ganglion tissue removed from the low thoracic/high lumbar region of a 32-year-old Caucasian male who died from acute pulmonary edema and bronchopneumonia, bilateral pleural and pericardial effusions, and malignant lymphoma (natural killer cell type). Patient history included probable cytomegalovirus infection, hepatic congestion and steatosis, splenomegaly, hemorrhagic cystitis, thyroid hemorrhage, and Bell's palsy.

Table 5

Program	Description	Reference	Parameter Threshold
ABI FACTURA	A program that removes vector sequences and masks ambiguous bases in nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA.	
ABI/PARACEL FDF	A Fast Data Finder useful in comparing and annotating amino acid or nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA; Paracel Inc., Pasadena, CA.	Mismatch <50%
ABI AutoAssembler	A program that assembles nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA.	
BLAST	A Basic Local Alignment Search Tool useful in sequence similarity search for amino acid and nucleic acid sequences. BLAST includes five functions: blastp, blastn, blastx, tblastn, and tblastx.	Altschul, S.F. et al. (1990) <i>J. Mol. Biol.</i> 215:403-410; Altschul, S.F. et al. (1997) <i>Nucleic Acids Res.</i> 25: 3389-3402.	ESTs: Probability value= 1.0E-8 or less Full Length sequences: Probability value= 1.0E-10 or less
FASTA	A Pearson and Lipman algorithm that searches for similarity between a query sequence and a group of sequences of the same type. FASTA comprises at least five functions: fasta, tfasta, fastx, tfastx, and ssearch.	Pearson, W.R. and D.J. Lipman (1988) <i>Proc. Natl. Acad. Sci.</i> 85:2444-2448; Pearson, W.R. (1990) <i>Methods Enzymol.</i> 183: 63-98; and Smith, T.F. and M. S. Waterman (1981) <i>Adv. Appl. Math.</i> 2:482-489.	ESTs: fasta E value=1.06E-6 Assembled ESTs: fasta Identity= 95% or greater and Match length=200 bases or greater; fastx E value=1.0E-8 or less Full Length sequences: fastx score=100 or greater
BLIMPS	A BLocks IMProved Searcher that matches a sequence against those in BLOCKS, PRINTS, DOMO, PRODOM, and PFAM databases to search for gene families, sequence homology, and structural fingerprint regions.	Henikoff, S and J.G. Henikoff, <i>Nucl. Acid Res.</i> , 19:6565-72, 1991. J.G. Henikoff and S. Henikoff (1996) <i>Methods Enzymol.</i> 266:88-105; and Attwood, T.K. et al. (1997) <i>J. Chem. Inf. Comput. Sci.</i> 37: 417-424.	Score=1000 or greater; Ratio of Score/Strength = 0.75 or larger; and, if applicable, Probability value= 1.0E-3 or less
HMMER	An algorithm for searching a query sequence against hidden Markov model (HMM)-based databases of protein family consensus sequences, such as PFAM.	Krogh, A. et al. (1994) <i>J. Mol. Biol.</i> , 235:1501-1531; Sonnhammer, E.L.L. et al. (1988) <i>Nucleic Acids Res.</i> 26:320-322.	Score=10-50 bits for PFAM hits, depending on individual protein families

Table 5 (cont.)

Program	Description	Reference	Parameter Threshold
ProfileScan	An algorithm that searches for structural and sequence motifs in protein sequences that match sequence patterns defined in Prosite.	Gribskov, M. et al. (1988) CABIOS 4:61-66; Gribskov, et al. (1989) Methods Enzymol. 183:146-159; Bairoch, A. et al. (1997) Nucleic Acids Res. 25: 217-221.	Normalized quality score \geq GCG-specified "HIGH" value for that particular Prosite motif. Generally, score=1.4-2.1.
Phred	A base-calling algorithm that examines automated sequencer traces with high sensitivity and probability.	Ewing, B. et al. (1998) Genome Res. 8:175-185; Ewing, B. and P. Green (1998) Genome Res. 8:186-194.	
Phrap	A Phils Revised Assembly Program including SWAT and CrossMatch, programs based on efficient implementation of the Smith-Waterman algorithm, useful in searching sequence homology and assembling DNA sequences.	Smith, T.F. and M. S. Waterman (1981) Adv. Appl. Math. 2:482-489; Smith, T.F. and M. S. Waterman (1981) J. Mol. Biol. 147:195-197; and Green, P., University of Washington, Seattle, WA.	Score= 120 or greater; Match length= 56 or greater
Consed	A graphical tool for viewing and editing Phrap assemblies	Gordon, D. et al. (1998) Genome Res. 8:195-202.	
SPScan	A weight matrix analysis program that scans protein sequences for the presence of secretory signal peptides.	Nielson, H. et al. (1997) Protein Engineering 10:1-6; Claverie, J.M. and S. Audic (1997) CABIOS 12: 431-439.	Score=3.5 or greater
Motifs	A program that searches amino acid sequences for patterns that matched those defined in Prosite.	Bairoch et al. <i>supra</i> ; Wisconsin Package Program Manual, version 9, page M51-59, Genetics Computer Group, Madison, WI.	

What is claimed is:

1. A substantially purified polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-31, and fragments thereof.
- 5 2. A substantially purified variant having at least 90% amino acid sequence identity to the amino acid sequence of claim 1.
3. An isolated and purified polynucleotide encoding the polypeptide of claim 1.
4. An isolated and purified polynucleotide variant having at least 80% polynucleotide sequence identity to the polynucleotide of claim 3.
- 10 5. An isolated and purified polynucleotide which hybridizes under stringent conditions to the polynucleotide of claim 3.
6. An isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide of claim 3.
7. A method for detecting a polynucleotide, the method comprising the steps of:
 - 15 (a) hybridizing the polynucleotide of claim 6 to at least one nucleic acid in a sample, thereby forming a hybridization complex; and
 - (b) detecting the hybridization complex, wherein the presence of the hybridization complex correlates with the presence of the polynucleotide in the sample.
8. The method of claim 7 further comprising amplifying the polynucleotide prior to
20 hybridization.
9. An isolated and purified polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:32-62 and fragments thereof.
10. An isolated and purified polynucleotide variant having at least 80% polynucleotide sequence identity to the polynucleotide of claim 9.
- 25 11. An isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide of claim 9.
12. An expression vector comprising at least a fragment of the polynucleotide of claim 3.
13. A host cell comprising the expression vector of claim 12.
- 30 14. A method for producing a polypeptide, the method comprising the steps of:
 - a) culturing the host cell of claim 13 under conditions suitable for the expression of the polypeptide; and
 - b) recovering the polypeptide from the host cell culture.
15. A pharmaceutical composition comprising the polypeptide of claim 1 in conjunction
35 with a suitable pharmaceutical carrier.
16. A purified antibody which specifically binds to the polypeptide of claim 1.

17. A purified agonist of the polypeptide of claim 1.
18. A purified antagonist of the polypeptide of claim 1.
19. A method for treating or preventing a disorder associated with decreased expression or activity of PHSP, the method comprising administering to a subject in need of such treatment an
5 effective amount of the pharmaceutical composition of claim 15.
20. A method for treating or preventing a disorder associated with increased expression or activity of PHSP, the method comprising administering to a subject in need of such treatment an effective amount of the antagonist of claim 18.

SEQUENCE LISTING

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<120> PHOSPHORYLATION EFFECTORS

<130> PF-0565 PCT

<140> To Be Assigned

<141> Herewith

<150> 09/123,494; unassigned; 09/152,814; unassigned; 09/173,482;
 unassigned; 60/106,889; 60/109,093; 60/113,796;

<151> 1998-07-28; 1998-07-28; 1998-09-14; 1998-09-14; 1998-10-14;
 1998-10-14; 1998-11-03; 1998-11-19; 1998-12-22

<160> 61

<170> PERL Program

<210> 1

<211> 300

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone Number: 132240

<400> 1

Met	Glu	Ser	Pro	Leu	Glu	Ser	Gln	Pro	Leu	Asp	Ser	Asp	Arg	Ser
1				5					10					15
Ile	Lys	Glu	Ser	Ser	Phe	Glu	Glu	Ser	Asn	Ile	Glu	Asp	Pro	Leu
			20						25					30
Ile	Val	Thr	Pro	Asp	Cys	Gln	Glu	Lys	Thr	Ser	Pro	Lys	Gly	Val
			35						40					45
Glu	Asn	Pro	Ala	Val	Gln	Glu	Ser	Asn	Gln	Lys	Met	Leu	Gly	Pro
			50						55					60
Pro	Leu	Glu	Val	Leu	Lys	Thr	Leu	Ala	Ser	Lys	Arg	Asn	Ala	Val
			65						70					75

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<210> 2
<211> 147
<212> PRT
<213> Homo sapiens
```

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<220>
<221> misc_feature
<223> Incyte Clone Number: 2180116
```

2/64

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Asp Phe Ile Gln Glu Leu Leu Ala Lys Leu Gln Gly Leu His Arg
      110                      115                      120
Gln Pro Gly Leu Arg Gln Pro Ser Pro Ser His Asp Gly Ser Leu
      125                      130                      135
Ser Pro Leu Gln Asp Arg Ala Arg Thr Ala His Pro
      140                      145

```

```

<210> 3
<211> 431
<212> PRT
<213> Homo sapiens

```

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<220>
<221> misc_feature
<223> Incyte Clone Number: 2197671

```

```

<400> 3
Met Ala His Ser Pro Val Gln Ser Gly Leu Pro Gly Met Gln Asn
  1          5          10          15
Leu Lys Ala Asp Pro Glu Glu Leu Phe Thr Lys Leu Glu Lys Ile
      20          25          30
Gly Lys Gly Ser Phe Gly Glu Val Phe Lys Gly Ile Asp Asn Arg
      35          40          45
Thr Gln Lys Val Val Ala Ile Lys Ile Ile Asp Leu Glu Glu Ala
      50          55          60
Glu Asp Glu Ile Glu Asp Ile Gln Gln Glu Ile Thr Val Leu Ser
      65          70          75
Gln Cys Asp Ser Pro Tyr Val Thr Lys Tyr Tyr Gly Ser Tyr Leu
      80          85          90
Lys Asp Thr Lys Leu Trp Ile Ile Met Glu Tyr Leu Gly Gly Gly
      95          100         105
Ser Ala Leu Asp Leu Leu Glu Pro Gly Arg Leu Asp Glu Thr Gln
      110         115         120
Ile Ala Thr Ile Leu Arg Glu Ile Leu Lys Gly Leu Asp Tyr Leu
      125         130         135
His Ser Glu Lys Lys Ile His Arg Asp Ile Lys Ala Ala Asn Val
      140         145         150
Leu Leu Ser Glu His Gly Glu Val Lys Leu Ala Asp Phe Gly Val
      155         160         165
Ala Gly Gln Leu Thr Asp Thr Gln Ile Lys Arg Asn Thr Phe Val
      170         175         180
Gly Thr Pro Phe Trp Met Ala Pro Glu Val Ile Lys Gln Ser Ala
      185         190         195
Tyr Asp Ser Lys Ala Asp Ile Trp Ser Leu Gly Ile Thr Ala Ile
      200         205         210
Glu Leu Ala Arg Gly Glu Pro Pro His Ser Glu Leu His Pro Met
      215         220         225
Lys Val Leu Phe Leu Ile Pro Lys Asn Asn Pro Pro Thr Leu Glu
      230         235         240
Gly Asn Tyr Ser Lys Pro Leu Lys Glu Phe Val Glu Ala Cys Leu
      245         250         255
Asn Lys Glu Pro Ser Phe Arg Pro Thr Ala Lys Glu Leu Leu Lys
      260         265         270
His Lys Phe Ile Leu Arg Asn Ala Lys Lys Thr Ser Tyr Leu Thr
      275         280         285

```

Glu	Leu	Ile	Asp	Arg	Tyr	Lys	Arg	Trp	Lys	Ala	Glu	Gln	Ser	His
									290					300
Asp	Asp	Ser	Ser	Ser	Glu	Asp	Ser	Asp	Ala	Glu	Thr	Asp	Gly	Gln
									305					315
Ala	Ser	Gly	Gly	Ser	Asp	Ser	Gly	Asp	Trp	Ile	Phe	Thr	Ile	Arg
									320					330
Glu	Lys	Asp	Pro	Lys	Asn	Leu	Glu	Asn	Gly	Ala	Leu	Gln	Pro	Ser
									335					345
Asp	Leu	Asp	Arg	Asn	Lys	Met	Lys	Asp	Ile	Pro	Lys	Arg	Pro	Phe
									350					360
Ser	Gln	Cys	Leu	Ser	Thr	Ile	Ile	Ser	Pro	Leu	Phe	Ala	Glu	Leu
									365					375
Lys	Glu	Lys	Ser	Gln	Ala	Cys	Gly	Gly	Asn	Leu	Gly	Ser	Ile	Glu
									380					390
Glu	Leu	Arg	Gly	Ala	Ile	Tyr	Leu	Ala	Glu	Glu	Ala	Cys	Pro	Gly
									395					405
Ile	Ser	Asp	Thr	Met	Val	Ala	Gln	Leu	Val	Gln	Arg	Leu	Gln	Arg
									410					420
Tyr	Ser	Leu	Ser	Gly	Gly	Gly	Thr	Ser	Ser	His				
									425					430

<210> 4

<211> 218

<212> PRT

<213> Homo sapiens

<220>

<221> misc feature

<223> Incyte Clone Number: 2594943

<400> 4

Met	Asn	Cys	Arg	Ser	Glu	Val	Leu	Glu	Val	Ser	Val	Glu	Gly	Arg
1				5					10					15
Gln	Val	Glu	Glu	Ala	Met	Leu	Ala	Val	Leu	His	Thr	Val	Leu	Leu
				20					25					30
His	Arg	Ser	Thr	Gly	Lys	Phe	His	Tyr	Lys	Lys	Glu	Gly	Thr	Tyr
				35					40					45
Ser	Ile	Gly	Thr	Val	Gly	Thr	Gln	Asp	Val	Asp	Cys	Asp	Phe	Ile
				50					55					60
Asp	Phe	Thr	Tyr	Val	Arg	Val	Ser	Ser	Glu	Glu	Leu	Asp	Arg	Ala
				65					70					75
Leu	Arg	Lys	Val	Val	Gly	Glu	Phe	Lys	Asp	Ala	Leu	Arg	Asn	Ser
				80					85					90
Gly	Gly	Asp	Gly	Leu	Gly	Gln	Met	Ser	Leu	Glu	Phe	Tyr	Gln	Lys
				95					100					105
Lys	Lys	Ser	Arg	Trp	Pro	Phe	Ser	Asp	Glu	Cys	Ile	Pro	Trp	Glu
				110					115					120
Val	Trp	Thr	Val	Lys	Val	His	Val	Val	Ala	Leu	Ala	Thr	Glu	Gln
				125					130					135
Glu	Arg	Gln	Ile	Cys	Arg	Glu	Lys	Val	Gly	Glu	Lys	Leu	Cys	Glu
				140					145					150
Lys	Ile	Ile	Asn	Ile	Val	Glu	Val	Met	Asn	Arg	His	Glu	Tyr	Leu
				155					160					165
Pro	Lys	Met	Pro	Thr	Gln	Ser	Glu	Val	Asp	Asn	Val	Phe	Asp	Thr
				170					175					180

Gly Leu Arg Asp Val Gln Pro Tyr Leu Tyr Lys Ile Ser Phe Gln
 185 190 195
 Ile Thr Asp Ala Leu Gly Thr Ser Val Thr Thr Thr Met Arg Arg
 200 205 210
 Leu Ile Lys Asp Thr Leu Ala Leu
 215

<210> 5
 <211> 474
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte Clone Number: 1513871

<400> 5
 Met Ile Met Asn Lys Met Lys Asn Phe Lys Arg Arg Phe Ser Leu
 1 5 10 15
 Ser Val Pro Arg Thr Glu Thr Ile Glu Glu Ser Leu Ala Glu Phe
 20 25 30
 Thr Glu Gln Phe Asn Gln Leu His Asn Arg Arg Asn Glu Asn Leu
 35 40 45
 Gln Leu Gly Pro Leu Gly Arg Asp Pro Pro Gln Glu Cys Ser Thr
 50 55 60
 Phe Ser Pro Thr Asp Ser Gly Glu Glu Pro Gly Gln Leu Ser Pro
 65 70 75
 Gly Val Gln Phe Gln Arg Arg Gln Asn Gln Arg Arg Phe Ser Met
 80 85 90
 Glu Asp Val Ser Lys Arg Leu Ser Leu Pro Met Asp Ile Arg Leu
 95 100 105
 Pro Gln Glu Phe Leu Gln Lys Leu Gln Met Glu Ser Pro Asp Leu
 110 115 120
 Pro Lys Pro Leu Ser Arg Met Ser Arg Arg Ala Ser Leu Ser Asp
 125 130 135
 Ile Gly Phe Gly Lys Leu Glu Thr Tyr Val Lys Leu Asp Lys Leu
 140 145 150
 Gly Glu Gly Thr Tyr Ala Thr Val Phe Lys Gly Arg Ser Lys Leu
 155 160 165
 Thr Glu Asn Leu Val Ala Leu Lys Glu Ile Arg Leu Glu His Glu
 170 175 180
 Glu Gly Ala Pro Cys Thr Ala Ile Arg Glu Val Ser Leu Leu Lys
 185 190 195
 Asn Leu Lys His Ala Asn Ile Val Thr Leu His Asp Leu Ile His
 200 205 210
 Thr Asp Arg Ser Leu Thr Leu Val Phe Glu Tyr Leu Asp Ser Asp
 215 220 225
 Leu Lys Gln Tyr Leu Asp His Cys Gly Asn Leu Met Ser Met His
 230 235 240
 Asn Val Lys Ile Phe Met Phe Gln Leu Leu Arg Gly Leu Ala Tyr
 245 250 255
 Cys His His Arg Lys Ile Leu His Arg Asp Leu Lys Pro Gln Asn
 260 265 270
 Leu Leu Ile Asn Glu Arg Gly Glu Leu Lys Leu Ala Asp Phe Gly
 275 280 285

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Leu Ala Arg Ala Lys Ser Val Pro Thr Lys Thr Tyr Ser Asn Glu
290 295 300
Val Val Thr Leu Trp Tyr Arg Pro Pro Asp Val Leu Leu Gly Ser
305 310 315
Thr Glu Tyr Ser Thr Pro Ile Asp Met Trp Gly Val Gly Cys Ile
320 325 330
His Tyr Glu Met Ala Thr Gly Arg Pro Leu Phe Pro Gly Ser Thr
335 340 345
Val Lys Glu Glu Leu His Leu Ile Phe Arg Leu Leu Gly Thr Pro
350 355 360
Thr Glu Glu Thr Trp Pro Gly Val Thr Ala Phe Ser Glu Phe Arg
365 370 375
Thr Tyr Ser Phe Pro Cys Tyr Leu Pro Gln Pro Leu Ile Asn His
380 385 390
Ala Pro Arg Leu Asp Thr Asp Gly Ile His Leu Leu Ser Ser Leu
395 400 405
Leu Leu Tyr Glu Ser Lys Ser Arg Met Ser Ala Glu Ala Ala Leu
410 415 420
Ser His Ser Tyr Phe Arg Ser Leu Gly Glu Arg Val His Gln Leu
425 430 435
Glu Asp Thr Ala Ser Ile Phe Ser Leu Lys Glu Ile Gln Leu Gln
440 445 450
Lys Asp Pro Gly Tyr Arg Gly Leu Ala Phe Gln Gln Pro Gly Arg
455 460 465
Gly Lys Asn Arg Arg Gln Ser Ile Phe
470

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<210> 6
<211> 540
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone Number: 156108

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<400> 6
Met Asn Gly Glu Ala Ile Cys Ser Ala Leu Pro Thr Ile Pro Tyr
1 5 10 15
His Lys Leu Ala Asp Leu Arg Tyr Leu Ser Arg Gly Ala Ser Gly
20 25 30
Thr Val Ser Ser Ala Arg His Ala Asp Trp Arg Val Gln Val Ala
35 40 45
Val Lys His Leu His Ile His Thr Pro Leu Leu Asp Ser Glu Arg
50 55 60
Lys Asp Val Leu Arg Glu Ala Glu Ile Leu His Lys Ala Arg Phe
65 70 75
Ser Tyr Ile Leu Pro Ile Leu Gly Ile Cys Asn Glu Pro Glu Phe
80 85 90
Leu Gly Ile Val Thr Glu Tyr Met Pro Asn Gly Ser Leu Asn Glu
95 100 105
Leu Leu His Arg Lys Thr Glu Tyr Pro Asp Val Ala Trp Pro Leu
110 115 120
Arg Phe Arg Ile Leu His Glu Ile Ala Leu Gly Val Asn Tyr Leu

```


	125		130		135
His Asn Met Thr Pro Pro Leu Leu His His Asp Leu Lys Thr Gln					
	140		145		150
Asn Ile Leu Leu Asp Asn Glu Phe His Val Lys Ile Ala Asp Phe					
	155		160		165
Gly Leu Ser Lys Trp Arg Met Met Ser Leu Ser Gln Ser Arg Ser					
	170		175		180
Ser Lys Ser Ala Pro Glu Gly Gly Thr Ile Ile Tyr Met Pro Pro					
	185		190		195
Glu Asn Tyr Glu Pro Gly Gln Lys Ser Arg Ala Ser Ile Lys His					
	200		205		210
Asp Ile Tyr Ser Tyr Ala Val Ile Thr Trp Glu Val Leu Ser Arg					
	215		220		225
Lys Gln Pro Phe Glu Asp Val Thr Asn Pro Leu Gln Ile Met Tyr					
	230		235		240
Ser Val Ser Gln Gly His Arg Pro Val Ile Asn Glu Glu Ser Leu					
	245		250		255
Pro Tyr Asp Ile Pro His Arg Ala Arg Met Ile Ser Leu Ile Glu					
	260		265		270
Ser Gly Trp Ala Gln Asn Pro Asp Glu Arg Pro Ser Phe Leu Lys					
	275		280		285
Cys Leu Ile Glu Leu Glu Pro Val Leu Arg Thr Phe Glu Glu Ile					
	290		295		300
Thr Phe Leu Glu Ala Val Ile Gln Leu Lys Lys Thr Lys Leu Gln					
	305		310		315
Ser Val Ser Ser Ala Ile His Leu Cys Asp Lys Lys Lys Met Glu					
	320		325		330
Leu Ser Leu Asn Ile Pro Val Asn His Gly Pro Gln Glu Glu Ser					
	335		340		345
Cys Gly Ser Ser Gln Leu His Glu Asn Ser Gly Ser Pro Glu Thr					
	350		355		360
Ser Arg Ser Leu Pro Ala Pro Gln Asp Asn Asp Phe Leu Ser Arg					
	365		370		375
Lys Ala Gln Asp Cys Tyr Phe Met Lys Leu His His Cys Pro Gly					
	380		385		390
Asn His Ser Trp Asp Ser Thr Ile Ser Gly Ser Gln Arg Ala Ala					
	395		400		405
Phe Cys Asp His Lys Thr Thr Pro Cys Ser Ser Ala Ile Ile Asn					
	410		415		420
Pro Leu Ser Thr Ala Gly Asn Ser Glu Arg Leu Gln Pro Gly Ile					
	425		430		435
Ala Gln Gln Trp Ile Gln Ser Lys Arg Glu Asp Ile Val Asn Gln					
	440		445		450
Met Thr Glu Ala Cys Leu Asn Gln Ser Leu Asp Ala Leu Leu Ser					
	455		460		465
Arg Asp Leu Ile Met Lys Glu Asp Tyr Glu Leu Val Ser Thr Lys					
	470		475		480
Pro Thr Arg Thr Ser Lys Val Arg Gln Leu Leu Asp Thr Thr Asp					
	485		490		495
Ile Gln Gly Glu Glu Phe Ala Lys Val Ile Val Gln Lys Leu Lys					
	500		505		510
Asp Asn Lys Gln Met Gly Leu Gln Pro Tyr Pro Glu Ile Leu Val					
	515		520		525
Val Ser Arg Ser Pro Ser Leu Asn Leu Leu Gln Asn Lys Ser Met					
	530		535		540

<210> 7
 <211> 454
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte Clone Number: 2883243

<400> 7

Met	Tyr	Asn	Thr	Val	Trp	Asn	Met	Glu	Asp	Leu	Asp	Leu	Glu	Tyr
1				5					10					15
Ala	Lys	Thr	Asp	Ile	Asn	Cys	Gly	Thr	Asp	Leu	Met	Phe	Tyr	Ile
				20					25					30
Glu	Met	Asp	Pro	Pro	Ala	Leu	Pro	Pro	Lys	Pro	Pro	Lys	Pro	Thr
				35					40					45
Thr	Val	Ala	Asn	Asn	Gly	Met	Asn	Asn	Asn	Met	Ser	Leu	Gln	Asp
				50					55					60
Ala	Glu	Trp	Tyr	Trp	Gly	Asp	Ile	Ser	Arg	Glu	Glu	Val	Asn	Glu
				65					70					75
Lys	Leu	Arg	Asp	Thr	Ala	Asp	Gly	Thr	Phe	Leu	Val	Arg	Asp	Ala
				80					85					90
Ser	Thr	Lys	Met	His	Gly	Asp	Tyr	Thr	Leu	Thr	Leu	Arg	Lys	Gly
				95					100					105
Gly	Asn	Asn	Lys	Leu	Ile	Lys	Ile	Phe	His	Arg	Asp	Gly	Lys	Tyr
				110					115					120
Gly	Phe	Ser	Asp	Pro	Leu	Thr	Phe	Ser	Ser	Val	Val	Glu	Leu	Ile
				125					130					135
Asn	His	Tyr	Arg	Asn	Glu	Ser	Leu	Ala	Gln	Tyr	Asn	Pro	Lys	Leu
				140					145					150
Asp	Val	Lys	Leu	Leu	Tyr	Pro	Val	Ser	Lys	Tyr	Gln	Gln	Asp	Gln
				155					160					165
Val	Val	Lys	Glu	Asp	Asn	Ile	Glu	Ala	Val	Gly	Lys	Lys	Leu	His
				170					175					180
Glu	Tyr	Asn	Thr	Gln	Phe	Gln	Glu	Lys	Ser	Arg	Glu	Tyr	Asp	Arg
				185					190					195
Leu	Tyr	Glu	Glu	Tyr	Thr	Arg	Thr	Ser	Gln	Glu	Ile	Gln	Met	Lys
				200					205					210
Arg	Thr	Ala	Ile	Glu	Ala	Phe	Asn	Glu	Thr	Ile	Lys	Ile	Phe	Glu
				215					220					225
Glu	Gln	Cys	Gln	Thr	Gln	Glu	Arg	Tyr	Ser	Lys	Glu	Tyr	Ile	Glu
				230					235					240
Lys	Phe	Lys	Arg	Glu	Gly	Asn	Glu	Lys	Glu	Ile	Gln	Arg	Ile	Met
				245					250					255
His	Asn	Tyr	Asp	Lys	Leu	Lys	Ser	Arg	Ile	Ser	Glu	Ile	Ile	Asp
				260					265					270
Ser	Arg	Arg	Arg	Leu	Glu	Glu	Asp	Leu	Lys	Lys	Gln	Ala	Ala	Glu
				275					280					285
Tyr	Arg	Glu	Ile	Asp	Lys	Arg	Met	Asn	Ser	Ile	Lys	Pro	Asp	Leu
				290					295					300
Ile	Gln	Leu	Arg	Lys	Thr	Arg	Asp	Gln	Tyr	Leu	Met	Trp	Leu	Thr
				305					310					315
Gln	Lys	Gly	Val	Arg	Gln	Lys	Lys	Leu	Asn	Glu	Trp	Leu	Gly	Asn
				320					325					330
Glu	Asn	Thr	Glu	Asp	Gln	Tyr	Ser	Leu	Val	Glu	Asp	Asp	Glu	Asp
				335					340					345

```

Leu Pro His His Asp Glu Lys Thr Trp Asn Val Gly Ser Ser Asn
      350      355      360
Arg Asn Lys Ala Glu Asn Leu Leu Arg Gly Lys Arg Asp Gly Thr
      365      370      375
Phe Leu Val Arg Glu Ser Ser Lys Gln Gly Cys Tyr Ala Cys Ser
      380      385      390
Val Val Val Asp Gly Glu Val Lys His Cys Val Ile Asn Lys Thr
      395      400      405
Ala Thr Gly Tyr Gly Phe Ala Glu Pro Tyr Asn Leu Tyr Ser Ser
      410      415      420
Leu Lys Glu Leu Val Leu His Tyr Gln His Thr Ser Leu Val Gln
      425      430      435
His Asn Asp Ser Leu Asn Val Thr Leu Ala Tyr Pro Val Tyr Ala
      440      445      450
Gln Gln Arg Arg

```

<210> 8

<211> 502

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone Number: 3173355

<400> 8

```

Met Phe Gly Thr Leu Leu Leu Tyr Cys Phe Phe Leu Ala Thr Val
  1      5      10      15
Pro Ala Leu Ala Glu Thr Gly Gly Glu Arg Gln Leu Ser Pro Glu
      20      25      30
Lys Ser Glu Ile Trp Gly Pro Gly Leu Lys Ala Asp Val Val Leu
      35      40      45
Pro Ala Arg Tyr Phe Tyr Ile Gln Ala Val Asp Thr Ser Gly Asn
      50      55      60
Lys Phe Thr Ser Ser Pro Gly Glu Lys Val Phe Gln Val Lys Val
      65      70      75
Ser Ala Pro Glu Glu Gln Phe Thr Arg Val Gly Val Gln Val Leu
      80      85      90
Asp Arg Lys Asp Gly Ser Phe Ile Val Arg Tyr Arg Met Tyr Ala
      95      100      105
Ser Tyr Lys Asn Leu Lys Val Glu Ile Lys Phe Gln Gly Gln His
      110      115      120
Val Ala Lys Ser Pro Tyr Ile Leu Lys Gly Pro Val Tyr His Glu
      125      130      135
Asn Cys Asp Cys Pro Leu Gln Asp Ser Ala Ala Trp Leu Arg Glu
      140      145      150
Met Asn Cys Pro Glu Thr Ile Ala Gln Ile Gln Arg Asp Leu Ala
      155      160      165
His Phe Pro Ala Val Asp Pro Glu Lys Ile Ala Val Glu Ile Pro
      170      175      180
Lys Arg Phe Gly Gln Arg Gln Ser Leu Cys His Tyr Thr Leu Lys
      185      190      195
Asp Asn Lys Val Tyr Ile Lys Thr His Gly Glu His Val Gly Phe
      200      205      210
Arg Ile Phe Met Asp Ala Ile Leu Leu Ser Leu Thr Arg Lys Val

```

	215		220		225
Lys Met Pro Asp	Val Glu Leu Phe Val	Asn Leu Gly Asp Trp	Pro		
	230		235		240
Leu Glu Lys Lys	Lys Ser Asn Ser Asn	Ile His Pro Ile Phe	Ser		
	245		250		255
Trp Cys Gly Ser	Thr Asp Ser Lys Asp	Ile Val Met Pro Thr	Tyr		
	260		265		270
Asp Leu Thr Asp	Ser Val Leu Glu Thr	Met Gly Arg Val Ser	Leu		
	275		280		285
Asp Met Met Ser	Val Gln Ala Asn Thr	Gly Pro Pro Trp Glu	Ser		
	290		295		300
Lys Asn Ser Thr	Ala Val Trp Arg Gly	Arg Asp Ser Arg Lys	Glu		
	305		310		315
Arg Leu Glu Leu	Val Lys Leu Ser Arg	Lys His Pro Glu Leu	Ile		
	320		325		330
Asp Ala Ala Phe	Thr Asn Phe Phe Phe	Phe Lys His Asp Glu	Asn		
	335		340		345
Leu Tyr Gly Pro	Ile Val Lys His Ile	Ser Phe Phe Asp Phe	Phe		
	350		355		360
Lys His Lys Tyr	Gln Ile Asn Ile Asp	Gly Thr Val Ala Ala	Tyr		
	365		370		375
Arg Leu Pro Tyr	Leu Leu Val Gly Asp	Ser Val Val Leu Lys	Gln		
	380		385		390
Asp Ser Ile Tyr	Tyr Glu His Phe Tyr	Asn Glu Leu Gln Pro	Trp		
	395		400		405
Lys His Tyr Ile	Pro Val Lys Ser Asn	Leu Ser Asp Leu Leu	Glu		
	410		415		420
Lys Leu Lys Trp	Ala Lys Asp His Asp	Glu Glu Ala Lys Lys	Ile		
	425		430		435
Ala Lys Ala Gly	Gln Glu Phe Ala Arg	Asn Asn Leu Met Gly	Asp		
	440		445		450
Asp Ile Phe Cys	Tyr Tyr Phe Lys Leu	Phe Gln Glu Tyr Ala	Asn		
	455		460		465
Leu Gln Val Ser	Glu Pro Gln Ile Arg	Glu Gly Met Lys Arg	Val		
	470		475		480
Glu Pro Gln Thr	Glu Asp Asp Leu Phe	Pro Cys Thr Cys His	Arg		
	485		490		495
Lys Lys Thr Lys	Asp Glu Leu				
	500				

<210> 9

<211> 282

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone Number: 5116906

<400> 9

Met Trp Ala Cys Gly Val Ile Leu Tyr	Ile Leu Leu Val Gly Tyr
1	5 10 15
Pro Pro Phe Trp Asp Glu Asp Gln His Arg Leu Tyr Gln Gln Ile	
20	25 30
Lys Ala Gly Ala Tyr Asp Phe Pro Ser Pro Glu Trp Asp Thr Val	
35	40 45

```

Thr Pro Glu Ala Lys Asp Leu Ile Asn Lys Met Leu Thr Ile Asn
      50                      55                      60
Pro Ala Lys Arg Ile Thr Ala Ser Glu Ala Leu Lys His Pro Trp
      65                      70                      75
Ile Cys Gln Arg Ser Thr Val Ala Ser Met Met His Arg Gln Glu
      80                      85                      90
Thr Val Asp Cys Leu Lys Lys Phe Asn Ala Arg Arg Lys Leu Lys
      95                      100                     105
Gly Ala Ile Leu Thr Thr Met Leu Ala Thr Arg Asn Phe Ser Ala
      110                     115                     120
Ala Lys Ser Leu Leu Lys Lys Pro Asp Gly Val Lys Glu Ser Thr
      125                     130                     135
Glu Ser Ser Asn Thr Thr Ile Glu Asp Glu Asp Val Lys Ala Arg
      140                     145                     150
Lys Gln Glu Ile Ile Lys Val Thr Glu Gln Leu Ile Glu Ala Ile
      155                     160                     165
Asn Asn Gly Asp Phe Glu Ala Tyr Thr Lys Ile Cys Asp Pro Gly
      170                     175                     180
Leu Thr Ala Phe Glu Pro Glu Ala Leu Gly Asn Leu Val Glu Gly
      185                     190                     195
Met Asp Phe His Arg Phe Tyr Phe Glu Asn Ala Leu Ser Lys Ser
      200                     205                     210
Asn Lys Pro Ile His Thr Ile Ile Leu Asn Pro His Val His Leu
      215                     220                     225
Val Gly Asp Asp Ala Ala Cys Ile Ala Tyr Ile Arg Leu Thr Gln
      230                     235                     240
Tyr Met Asp Gly Ser Gly Met Pro Lys Thr Met Gln Ser Glu Glu
      245                     250                     255
Thr Arg Val Trp His Arg Arg Asp Gly Lys Trp Gln Asn Val His
      260                     265                     270
Phe His Arg Ser Gly Ser Pro Thr Val Pro Ile Asn
      275                     280

```

```

<210> 10
<211> 510
<212> PRT
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone Number: 940589

```

```

<400> 10
Met Lys Ala Asp Ile Lys Ile Trp Ile Leu Thr Gly Asp Lys Gln
  1                      5                      10                     15
Glu Thr Ala Ile Asn Ile Gly His Ser Cys Lys Leu Leu Lys Lys
      20                      25                      30
Asn Met Gly Met Ile Val Ile Asn Glu Gly Ser Leu Asp Ser Phe
      35                      40                      45
Ser Asn Thr Gln Asn Ser Arg Lys Glu Ala Val Leu Leu Ala Lys
      50                      55                      60
Met Lys His Pro Asn Ile Val Ala Phe Lys Glu Ser Phe Glu Ala
      65                      70                      75
Glu Gly His Leu Tyr Ile Val Met Glu Tyr Cys Asp Gly Gly Asp
      80                      85                      90

```

Leu Met Gln Lys	Ile Lys Gln Gln Lys	Gly Lys Leu Phe Pro	Glu
95	100		105
Asp Met Ile Leu	Asn Trp Phe Thr Gln	Met Cys Leu Gly Val	Asn
110	115		120
His Ile His Lys	Lys Arg Val Leu His	Arg Asp Ile Lys Ser	Lys
125	130		135
Asn Ile Phe Leu	Thr Gln Asn Gly Lys	Val Lys Leu Gly Asp	Phe
140	145		150
Gly Ser Ala Arg	Leu Leu Ser Asn Pro	Met Ala Phe Ala Cys	Thr
155	160		165
Tyr Val Gly Thr	Pro Tyr Tyr Val Pro	Pro Glu Ile Trp Glu	Asn
170	175		180
Leu Pro Tyr Asn	Asn Lys Ser Asp Ile	Trp Ser Leu Gly Cys	Ile
185	190		195
Leu Tyr Glu Leu	Cys Thr Leu Lys His	Pro Phe Gln Ala Asn	Ser
200	205		210
Trp Lys Asn Leu	Ile Leu Lys Val Cys	Gln Gly Cys Ile Ser	Pro
215	220		225
Leu Pro Ser His	Tyr Ser Tyr Glu Leu	Gln Phe Leu Val Lys	Gln
230	235		240
Met Phe Lys Arg	Asn Pro Ser His Arg	Pro Ser Ala Thr Thr	Leu
245	250		255
Leu Ser Arg Gly	Ile Val Ala Arg Leu	Val Gln Lys Cys Leu	Pro
260	265		270
Pro Glu Ile Ile	Met Glu Tyr Gly Glu	Glu Val Leu Glu Glu	Ile
275	280		285
Lys Asn Ser Lys	His Asn Thr Pro Arg	Lys Lys Thr Asn Pro	Ser
290	295		300
Arg Ile Arg Ile	Ala Leu Gly Asn Glu	Ala Ser Thr Val Gln	Glu
305	310		315
Glu Glu Gln Asp	Arg Lys Gly Ser His	Thr Asp Leu Glu Ser	Ile
320	325		330
Asn Glu Asn Leu	Val Glu Ser Ala Leu	Arg Arg Val Asn Arg	Glu
335	340		345
Glu Lys Gly Asn	Lys Ser Val His Leu	Arg Lys Ala Ser Ser	Pro
350	355		360
Asn Leu His Arg	Arg Gln Trp Glu Lys	Asn Val Pro Asn Thr	Ala
365	370		375
Leu Thr Ala Leu	Glu Asn Ala Ser Ile	Leu Thr Ser Ser Leu	Thr
380	385		390
Ala Glu Asp Asp	Arg Gly Gly Ser Val	Ile Lys Tyr Ser Lys	Asn
395	400		405
Thr Thr Arg Lys	Gln Trp Leu Lys Glu	Thr Pro Asp Thr Leu	Leu
410	415		420
Asn Ile Leu Lys	Asn Ala Asp Leu Ser	Leu Ala Phe Gln Thr	Tyr
425	430		435
Thr Ile Tyr Arg	Pro Gly Ser Glu Gly	Phe Leu Lys Gly Pro	Leu
440	445		450
Ser Glu Glu Thr	Glu Ala Ser Asp Ser	Val Asp Gly Gly His	Asp
455	460		465
Ser Val Ile Leu	Asp Pro Glu Arg Leu	Glu Pro Gly Leu Asp	Glu
470	475		480
Glu Asp Thr Asp	Phe Glu Glu Glu Asp	Asp Asn Pro Asp Trp	Val
485	490		495
Ser Glu Leu Lys	Lys Arg Ala Gly Trp	Gln Gly Leu Cys Asp	Arg
500	505		510

<210> 11
 <211> 248
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte Clone Number: 304421

<400> 11
 Met Ala Glu Thr Ser Leu Pro Glu Leu Gly Gly Glu Asp Lys Ala
 1 5 10 15
 Thr Pro Cys Pro Ser Ile Leu Glu Leu Glu Glu Leu Leu Arg Ala
 20 25 30
 Gly Lys Ser Ser Cys Ser Arg Val Asp Glu Val Trp Pro Asn Leu
 35 40 45
 Phe Ile Gly Asp Ala Met Asp Ser Leu Gln Lys Gln Asp Leu Arg
 50 55 60
 Arg Pro Lys Ile His Gly Ala Val Gln Ala Ser Pro Tyr Gln Pro
 65 70 75
 Pro Thr Leu Ala Ser Leu Gln Arg Leu Leu Trp Val Arg Gln Ala
 80 85 90
 Ala Thr Leu Asn His Ile Asp Glu Val Trp Pro Ser Leu Phe Leu
 95 100 105
 Gly Asp Ala Tyr Ala Ala Arg Asp Lys Ser Lys Leu Ile Gln Leu
 110 115 120
 Gly Ile Thr His Val Val Asn Ala Ala Ala Gly Lys Phe Gln Val
 125 130 135
 Asp Thr Gly Ala Lys Phe Tyr Arg Gly Met Ser Leu Glu Tyr Tyr
 140 145 150
 Gly Ile Glu Ala Asp Asp Asn Pro Phe Phe Asp Leu Ser Val Tyr
 155 160 165
 Phe Leu Pro Val Ala Arg Tyr Ile Arg Ala Ala Leu Ser Val Pro
 170 175 180
 Gln Gly Arg Val Leu Val His Cys Ala Met Gly Val Ser Arg Ser
 185 190 195
 Ala Thr Leu Val Leu Ala Phe Leu Met Ile Tyr Glu Asn Met Thr
 200 205 210
 Leu Val Glu Ala Ile Gln Thr Val Gln Ala His Arg Asn Ile Cys
 215 220 225
 Pro Asn Ser Gly Phe Leu Arg Gln Leu Gln Val Leu Asp Asn Arg
 230 235 240
 Leu Gly Arg Glu Thr Gly Arg Phe
 245

<210> 12
 <211> 810
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte Clone Number: 1213802

<400> 12

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Met Pro Asn Gln Gly Glu Asp Cys Tyr Phe Phe Phe Tyr Ser Thr
 1                               5 10 15
Cys Thr Lys Gly Asp Ser Cys Pro Phe Arg His Cys Glu Ala Ala
 20 25 30
Ile Gly Asn Glu Thr Val Cys Thr Leu Trp Gln Glu Gly Arg Cys
 35 40 45
Phe Arg Gln Val Cys Arg Phe Arg His Met Glu Ile Asp Lys Lys
 50 55 60
Arg Ser Glu Ile Pro Cys Tyr Trp Glu Asn Gln Pro Thr Gly Cys
 65 70 75
Gln Lys Leu Asn Cys Ala Phe His His Asn Arg Gly Arg Tyr Val
 80 85 90
Asp Gly Leu Phe Leu Pro Pro Ser Lys Thr Val Leu Pro Thr Val
 95 100 105
Pro Glu Ser Pro Glu Glu Glu Val Lys Ala Ser Gln Leu Ser Val
 110 115 120
Gln Gln Asn Lys Leu Ser Val Gln Ser Asn Pro Ser Pro Gln Leu
 125 130 135
Arg Ser Val Met Lys Val Glu Ser Ser Glu Asn Val Pro Ser Pro
 140 145 150
Thr His Pro Pro Val Val Ile Asn Ala Ala Asp Asp Asp Glu Asp
 155 160 165
Asp Asp Asp Gln Phe Ser Glu Glu Gly Asp Glu Thr Lys Thr Pro
 170 175 180
Thr Leu Gln Pro Thr Pro Glu Val His Asn Gly Leu Arg Val Thr
 185 190 195
Ser Val Arg Lys Pro Ala Val Asn Ile Lys Gln Gly Glu Cys Leu
 200 205 210
Asn Phe Gly Ile Lys Thr Leu Glu Glu Ile Lys Ser Lys Lys Met
 215 220 225
Lys Glu Lys Ser Lys Lys Gln Gly Glu Gly Ser Ser Gly Val Ser
 230 235 240
Ser Leu Leu Leu His Pro Glu Pro Val Pro Gly Pro Glu Lys Glu
 245 250 255
Asn Val Arg Thr Val Val Arg Thr Val Thr Leu Ser Thr Lys Gln
 260 265 270
Gly Glu Glu Pro Leu Val Arg Leu Ser Leu Thr Glu Arg Leu Gly
 275 280 285
Lys Arg Lys Phe Ser Ala Gly Gly Asp Ser Asp Pro Pro Leu Lys
 290 295 300
Arg Ser Leu Ala Gln Arg Leu Gly Lys Lys Val Glu Ala Pro Glu
 305 310 315
Thr Asn Ile Asp Lys Thr Pro Lys Lys Ala Gln Val Ser Lys Ser
 320 325 330
Leu Lys Glu Arg Leu Gly Met Ser Ala Asp Pro Asp Asn Glu Asp
 335 340 345
Ala Thr Asp Lys Val Asn Lys Val Gly Glu Ile His Val Lys Thr
 350 355 360
Leu Glu Glu Ile Leu Leu Glu Arg Ala Ser Gln Lys Arg Gly Glu
 365 370 375
Leu Gln Thr Lys Leu Lys Thr Glu Gly Pro Ser Lys Thr Asp Asp
 380 385 390
Ser Thr Ser Gly Ala Arg Ser Ser Ser Thr Ile Arg Ile Lys Thr
 395 400 405
Phe Ser Glu Val Leu Ala Glu Lys Lys His Arg Gln Gln Glu Ala

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410	415	420
Glu Arg Gln Lys Ser Lys Lys Asp Thr Thr Cys Ile Lys Leu Lys		
425	430	435
Ile Asp Ser Glu Ile Lys Lys Thr Val Val Leu Pro Pro Ile Val		
440	445	450
Ala Ser Arg Gly Gln Ser Glu Glu Pro Ala Gly Lys Thr Lys Ser		
455	460	465
Met Gln Glu Val His Ile Lys Thr Leu Glu Glu Ile Lys Leu Glu		
470	475	480
Lys Ala Leu Arg Val Gln Gln Ser Ser Glu Ser Ser Thr Ser Ser		
485	490	495
Pro Ser Gln His Glu Ala Thr Pro Gly Ala Arg Arg Leu Leu Arg		
500	505	510
Ile Thr Lys Arg Thr Gly Met Lys Glu Glu Lys Asn Leu Gln Glu		
515	520	525
Gly Asn Glu Val Asp Ser Gln Ser Ser Ile Arg Thr Glu Ala Lys		
530	535	540
Glu Ala Ser Gly Glu Thr Thr Gly Val Asp Ile Thr Lys Ile Gln		
545	550	555
Val Lys Arg Cys Glu Thr Met Arg Glu Lys His Met Gln Lys Gln		
560	565	570
Gln Glu Arg Glu Lys Ser Val Leu Thr Pro Leu Arg Gly Asp Val		
575	580	585
Ala Ser Cys Asn Thr Gln Val Ala Glu Lys Pro Val Leu Thr Ala		
590	595	600
Val Pro Gly Ile Thr Arg His Leu Thr Lys Arg Leu Pro Thr Lys		
605	610	615
Ser Ser Gln Lys Val Glu Val Glu Thr Ser Gly Ile Gly Asp Ser		
620	625	630
Leu Leu Asn Val Lys Cys Ala Ala Gln Thr Leu Glu Lys Arg Gly		
635	640	645
Lys Ala Lys Pro Lys Val Asn Val Lys Pro Ser Val Val Lys Val		
650	655	660
Val Ser Ser Pro Lys Leu Ala Pro Lys Arg Lys Ala Val Glu Met		
665	670	675
His Ala Ala Val Ile Ala Ala Val Lys Pro Leu Ser Ser Ser Ser		
680	685	690
Val Leu Gln Glu Pro Pro Ala Lys Lys Ala Ala Val Ala Val Val		
695	700	705
Pro Leu Val Ser Glu Asp Lys Ser Val Thr Val Pro Glu Ala Glu		
710	715	720
Asn Pro Arg Asp Ser Leu Val Leu Pro Pro Thr Gln Ser Ser Ser		
725	730	735
Asp Ser Ser Pro Pro Glu Val Ser Gly Pro Ser Ser Ser Gln Met		
740	745	750
Ser Met Lys Thr Arg Arg Leu Ser Ser Ala Ser Thr Gly Lys Pro		
755	760	765
Pro Leu Ser Val Glu Asp Asp Phe Glu Lys Leu Ile Trp Glu Ile		
770	775	780
Ser Gly Gly Lys Leu Glu Ala Glu Ile Asp Leu Asp Pro Gly Lys		
785	790	795
Asp Glu Asp Asp Leu Leu Leu Glu Leu Ser Glu Met Ile Asp Ser		
800	805	810

<211> 549

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone Number: 1378134

<400> 13

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Met Arg Arg Arg Ala Ser Asn Ala Ala Ala Ala His Thr Ile
 1              5              10              15
Gly Gly Ser Lys His Thr Met Asn Asp His Leu His Val Gly Ser
      20              25              30
His Ala His Gly Gln Ile Gln Val Arg Gln Leu Phe Glu Asp Asn
      35              40              45
Ser Asn Lys Arg Thr Val Leu Thr Thr Gln Pro Asn Gly Leu Thr
      50              55              60
Thr Val Gly Lys Thr Gly Leu Pro Val Val Pro Glu Arg Gln Leu
      65              70              75
Asp Ser Ile His Arg Arg Gln Gly Ser Ser Thr Ser Leu Lys Ser
      80              85              90
Met Glu Gly Met Gly Lys Val Lys Ala Thr Pro Met Thr Pro Glu
      95              100             105
Gln Ala Met Lys Gln Tyr Met Gln Lys Leu Thr Ala Phe Glu His
      110             115             120
His Glu Ile Phe Ser Tyr Pro Glu Ile Tyr Phe Leu Gly Leu Asn
      125             130             135
Ala Lys Lys Arg Gln Gly Met Thr Gly Gly Pro Asn Asn Gly Gly
      140             145             150
Tyr Asp Asp Asp Gln Gly Ser Tyr Val Gln Val Pro His Asp His
      155             160             165
Val Ala Tyr Arg Tyr Glu Val Leu Lys Val Ile Gly Lys Gly Ser
      170             175             180
Phe Gly Gln Val Val Lys Ala Tyr Asp His Lys Val His Gln His
      185             190             195
Val Ala Leu Lys Met Val Arg Asn Glu Lys Arg Phe His Arg Gln
      200             205             210
Ala Ala Glu Glu Ile Arg Ile Leu Glu His Leu Arg Lys Gln Asp
      215             220             225
Lys Asp Asn Thr Met Asn Val Ile His Met Leu Glu Asn Phe Thr
      230             235             240
Phe Arg Asn His Ile Cys Met Thr Phe Glu Leu Leu Ser Met Asn
      245             250             255
Leu Tyr Glu Leu Ile Lys Lys Asn Lys Phe Gln Gly Phe Ser Leu
      260             265             270
Pro Leu Val Arg Lys Phe Ala His Ser Ile Leu Gln Cys Leu Asp
      275             280             285
Ala Leu His Lys Asn Arg Ile Ile His Cys Asp Leu Lys Pro Glu
      290             295             300
Asn Ile Leu Leu Lys Gln Gln Gly Arg Ser Gly Ile Lys Val Ile
      305             310             315
Asp Phe Gly Ser Ser Cys Tyr Glu His Gln Arg Val Tyr Thr Tyr
      320             325             330
Ile Gln Ser Arg Phe Tyr Arg Ala Pro Glu Val Ile Leu Gly Ala
      335             340             345
Arg Tyr Gly Met Pro Ile Asp Met Trp Ser Leu Gly Cys Ile Leu

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350	355	360
Ala Glu Leu Leu Thr Gly Tyr Pro Leu Leu Pro Gly Glu Asp Glu		
365	370	375
Gly Asp Gln Leu Ala Cys Met Ile Glu Leu Leu Gly Met Pro Ser		
380	385	390
Gln Lys Leu Leu Asp Ala Ser Lys Arg Ala Lys Asn Phe Val Ser		
395	400	405
Ser Lys Gly Tyr Pro Arg Tyr Cys Thr Val Thr Thr Leu Ser Asp		
410	415	420
Gly Ser Val Val Leu Asn Gly Gly Arg Ser Arg Arg Gly Lys Leu		
425	430	435
Arg Gly Pro Pro Glu Ser Arg Glu Trp Gly Asn Ala Leu Lys Gly		
440	445	450
Cys Asp Asp Pro Leu Phe Leu Asp Phe Leu Lys Gln Cys Leu Glu		
455	460	465
Trp Asp Pro Ala Val Arg Met Thr Pro Gly Gln Ala Leu Arg His		
470	475	480
Pro Trp Leu Arg Arg Arg Leu Pro Lys Pro Pro Thr Gly Glu Lys		
485	490	495
Thr Ser Val Lys Arg Ile Thr Glu Ser Thr Gly Ala Ile Thr Ser		
500	505	510
Ile Ser Lys Leu Pro Pro Pro Ser Ser Ser Ala Ser Lys Leu Arg		
515	520	525
Thr Asn Leu Ala Gln Met Thr Asp Ala Asn Gly Asn Ile Gln Gln		
530	535	540
Arg Thr Val Leu Pro Lys Leu Val Ser		
545		

<210> 14

<211> 416

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone Number: 1490070

<400> 14

Met Met Pro Gln Leu Gln Phe Lys Asp Ala Phe Trp Cys Arg Asp		
1	5	10
Phe Thr Ala His Thr Gly Tyr Glu Val Leu Leu Gln Arg Leu Leu		15
	20	25
Asp Gly Arg Lys Met Cys Lys Asp Met Val Glu Leu Leu Trp Gln		30
	35	40
Arg Ala Gln Ala Glu Glu Arg Tyr Gly Lys Glu Leu Val Gln Ile		45
	50	55
Ala Arg Lys Ala Gly Gly Gln Thr Glu Ile Asn Ser Leu Arg Ala		60
	65	70
Ser Phe Asp Ser Leu Lys Gln Gln Met Glu Asn Val Gly Ser Ser		75
	80	85
His Ile Gln Leu Ala Leu Thr Leu Arg Glu Glu Leu Arg Ser Leu		90
	95	100
Glu Glu Phe Arg Glu Arg Gln Lys Glu Gln Arg Lys Lys Tyr Glu		105
	110	115
Ala Val Met Asp Arg Val Gln Lys Ser Lys Leu Ser Leu Tyr Lys		120

	125		130		135
Lys Ala Met Glu Ser Lys Lys Thr Tyr Glu Gln Lys Cys Arg Asp					
	140		145		150
Ala Asp Asp Ala Glu Gln Ala Phe Glu Arg Ile Ser Ala Asn Gly					
	155		160		165
His Gln Lys Gln Val Glu Lys Ser Gln Asn Lys Ala Arg Gln Cys					
	170		175		180
Lys Asp Ser Ala Thr Glu Ala Glu Arg Val Tyr Arg Gln Ser Ile					
	185		190		195
Ala Gln Leu Glu Lys Val Arg Ala Glu Trp Glu Gln Glu His Arg					
	200		205		210
Thr Thr Cys Glu Ala Phe Gln Leu Gln Glu Phe Asp Arg Leu Thr					
	215		220		225
Ile Leu Arg Asn Ala Leu Trp Val His Ser Asn Gln Leu Ser Met					
	230		235		240
Gln Cys Val Lys Asp Asp Glu Leu Tyr Glu Glu Val Arg Leu Thr					
	245		250		255
Leu Glu Gly Cys Ser Ile Asp Ala Asp Ile Asp Ser Phe Ile Gln					
	260		265		270
Ala Lys Ser Thr Gly Thr Glu Pro Pro Ala Pro Val Pro Tyr Gln					
	275		280		285
Asn Tyr Tyr Asp Arg Glu Val Thr Pro Leu Thr Ser Ser Pro Gly					
	290		295		300
Ile Gln Pro Ser Cys Gly Met Ile Lys Arg Phe Ser Gly Leu Leu					
	305		310		315
His Gly Ser Pro Lys Thr Thr Ser Leu Ala Ala Ser Ala Ala Ser					
	320		325		330
Thr Glu Thr Leu Thr Pro Thr Pro Glu Arg Asn Glu Gly Val Tyr					
	335		340		345
Thr Ala Ile Ala Val Gln Glu Ile Gln Gly Asn Pro Ala Ser Pro					
	350		355		360
Ala Gln Glu Tyr Arg Ala Leu Tyr Asp Tyr Thr Ala Gln Asn Pro					
	365		370		375
Asp Glu Leu Asp Leu Ser Ala Gly Asp Ile Leu Glu Val Ile Leu					
	380		385		390
Glu Gly Glu Asp Gly Trp Trp Thr Val Glu Arg Asn Gly Gln Arg					
	395		400		405
Gly Phe Val Pro Gly Ser Tyr Leu Glu Lys Leu					
	410		415		

<210> 15

<211> 425

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone Number: 1997814

<400> 15

Met Glu Gln Gly Leu Glu Glu Glu Glu Glu Val Asp Pro Arg Ile			
1	5	10	15
Gln Gly Glu Leu Glu Lys Leu Asn Gln Ser Thr Asp Asp Ile Asn			
	20	25	30
Arg Arg Glu Thr Glu Leu Glu Asp Ala Arg Gln Lys Phe Arg Ser			
	35	40	45

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Val Leu Val Glu Ala Thr Val Lys Leu Asp Glu Leu Val Lys Lys
      50                      55                      60
Ile Gly Lys Ala Val Glu Asp Ser Lys Pro Tyr Trp Glu Ala Arg
      65                      70                      75
Arg Val Ala Arg Gln Ala Gln Leu Glu Ala Gln Lys Ala Thr Gln
      80                      85                      90
Asp Phe Gln Arg Ala Thr Glu Val Leu Arg Ala Ala Lys Glu Thr
      95                      100                     105
Ile Ser Leu Ala Glu Gln Arg Leu Leu Glu Asp Asp Lys Arg Gln
     110                      115                     120
Phe Asp Ser Ala Trp Gln Glu Met Leu Asn His Ala Thr Gln Arg
     125                      130                     135
Val Met Glu Ala Glu Gln Thr Lys Thr Arg Ser Glu Leu Val His
     140                      145                     150
Lys Glu Thr Ala Ala Arg Tyr Asn Ala Ala Met Gly Arg Met Arg
     155                      160                     165
Gln Leu Glu Lys Lys Leu Lys Arg Ala Ile Asn Lys Ser Lys Pro
     170                      175                     180
Tyr Phe Glu Leu Lys Ala Lys Tyr Tyr Val Gln Leu Glu Gln Leu
     185                      190                     195
Lys Lys Thr Val Asp Asp Leu Gln Ala Lys Leu Thr Leu Ala Lys
     200                      205                     210
Gly Glu Tyr Lys Met Ala Leu Lys Asn Leu Glu Met Ile Ser Asp
     215                      220                     225
Glu Ile His Glu Arg Arg Arg Ser Ser Ala Met Gly Pro Arg Gly
     230                      235                     240
Cys Gly Val Gly Ala Glu Gly Ser Ser Thr Ser Val Glu Asp Leu
     245                      250                     255
Pro Gly Ser Lys Pro Glu Pro Asp Ala Ile Ser Val Ala Ser Glu
     260                      265                     270
Ala Phe Glu Asp Asp Ser Cys Ser Asn Phe Val Ser Glu Asp Asp
     275                      280                     285
Ser Glu Thr Gln Ser Val Ser Ser Phe Ser Ser Gly Pro Thr Ser
     290                      295                     300
Pro Ser Glu Met Pro Asp Gln Phe Pro Ala Val Val Arg Pro Gly
     305                      310                     315
Ser Leu Asp Leu Pro Ser Pro Val Ser Leu Ser Glu Phe Gly Met
     320                      325                     330
Met Phe Pro Val Leu Gly Pro Arg Ser Glu Cys Ser Gly Ala Ser
     335                      340                     345
Ser Pro Glu Cys Glu Val Glu Arg Gly Asp Arg Ala Glu Gly Ala
     350                      355                     360
Glu Asn Lys Thr Ser Asp Lys Ala Asn Asn Asn Arg Gly Leu Ser
     365                      370                     375
Ser Ser Ser Gly Ser Gly Gly Ser Ser Lys Ser Gln Ser Ser Thr
     380                      385                     390
Ser Pro Glu Gly Gln Ala Leu Glu Asn Arg Met Lys Gln Leu Ser
     395                      400                     405
Leu Gln Cys Ser Lys Gly Arg Asp Gly Ile Ile Ala Asp Ile Lys
     410                      415                     420
Met Val Gln Ile Gly
     425

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<210> 16

<211> 1135

<213> Homo sapiens

<221> misc feature

<223> Incyte Clone Number: 2299715

Met	Ala	Asn	Asp	Ser	Pro	Ala	Lys	Ser	Leu	Val	Asp	Ile	Asp	Leu
1				5					10					15
Ser	Ser	Leu	Arg	Asp	Pro	Ala	Gly	Ile	Phe	Glu	Leu	Val	Glu	Val
				20					25					30
Val	Gly	Asn	Gly	Thr	Tyr	Gly	Gln	Val	Tyr	Lys	Gly	Arg	His	Val
				35					40					45
Lys	Thr	Gly	Gln	Leu	Ala	Ala	Ile	Lys	Val	Met	Asp	Val	Thr	Glu
				50					55					60

Asp	Glu	Glu	Glu	Glu	Ile	Lys	Leu	Glu	Ile	Asn	Met	Leu	Lys	Lys
				65					70					75
Tyr	Ser	His	His	Arg	Asn	Ile	Ala	Thr	Tyr	Tyr	Gly	Ala	Phe	Ile
				80					85					90
Lys	Lys	Ser	Pro	Pro	Gly	His	Asp	Asp	Gln	Leu	Trp	Leu	Val	Met
				95					100					105
Glu	Phe	Cys	Gly	Ala	Gly	Ser	Ile	Thr	Asp	Leu	Val	Lys	Asn	Thr
				110					115					120
Lys	Gly	Asn	Thr	Leu	Lys	Glu	Asp	Trp	Ile	Ala	Tyr	Ile	Ser	Arg
				125					130					135
Glu	Ile	Leu	Arg	Gly	Leu	Ala	His	Leu	His	Ile	His	His	Val	Ile
				140					145					150
His	Arg	Asp	Ile	Lys	Gly	Gln	Asn	Val	Leu	Leu	Thr	Glu	Asn	Ala
				155					160					165
Gly	Val	Lys	Leu	Val	Asp	Phe	Gly	Val	Ser	Ala	Gln	Leu	Asp	Arg
				170					175					180
Thr	Val	Gly	Arg	Arg	Asn	Thr	Phe	Ile	Gly	Thr	Pro	Tyr	Trp	Met
				185					190					195
Ala	Pro	Glu	Val	Ile	Ala	Cys	Asp	Glu	Asn	Pro	Asp	Ala	Thr	Tyr
				200					205					210
Asp	Tyr	Arg	Ser	Asp	Leu	Trp	Ser	Cys	Gly	Ile	Thr	Ala	Ile	Glu
				215					220					225
Met	Ala	Glu	Gly	Ala	Pro	Pro	Leu	Cys	Asp	Met	His	Pro	Met	Arg
				230					235					240
Ala	Leu	Phe	Leu	Ile	Pro	Arg	Asn	Pro	Pro	Pro	Arg	Leu	Lys	Ser
				245					250					255
Lys	Lys	Trp	Ser	Lys	Lys	Phe	Phe	Ser	Phe	Ile	Glu	Gly	Cys	Leu
				260					265					270
Val	Lys	Asn	Tyr	Met	Gln	Arg	Pro	Ser	Thr	Glu	Gln	Leu	Leu	Lys
				275					280					285
His	Pro	Phe	Ile	Arg	Asp	Gln	Pro	Asn	Glu	Arg	Gln	Val	Arg	Ile
				290					295					300
Gln	Leu	Lys	Asp	His	Ile	Asp	Arg	Thr	Arg	Lys	Lys	Arg	Gly	Glu
				305					310					315
Lys	Asp	Glu	Thr	Glu	Tyr	Glu	Tyr	Ser	Gly	Ser	Glu	Glu	Glu	Glu
				320					325					330
Glu	Glu	Val	Pro	Glu	Gln	Glu	Gly	Glu	Pro	Ser	Ser	Ile	Val	Asn
				335					340					345
Val	Pro	Gly	Glu	Ser	Thr	Leu	Arg	Arg	Asp	Phe	Leu	Arg	Leu	Glu

Gln Glu Asn Lys	350	355	360
Glu Arg Ser Glu Ala		Leu Arg Arg Gln Gln Leu	
365		370	375
Leu Gln Glu Gln Gln Leu Arg Glu Gln		Glu Glu Tyr Lys Arg Gln	
380		385	390
Leu Leu Ala Glu Arg Gln Lys Arg Ile		Glu Gln Gln Lys Glu Gln	
395		400	405
Arg Arg Arg Leu Glu Glu Gln Gln Arg		Arg Glu Arg Glu Ala Arg	
410		415	420
Arg Gln Gln Glu Arg Glu Gln Arg Arg		Arg Glu Gln Glu Glu Lys	
425		430	435
Arg Arg Leu Glu Glu Leu Glu Arg Arg		Arg Lys Glu Glu Glu Glu	
440		445	450
Arg Arg Arg Ala Glu Glu Glu Lys Arg		Arg Val Glu Arg Glu Gln	
455		460	465
Glu Tyr Ile Arg Arg Gln Leu Glu Glu		Glu Gln Arg His Leu Glu	
470		475	480
Val Leu Gln Gln Gln Leu Leu Gln Glu		Gln Ala Met Leu Leu His	
485		490	495
Asp His Arg Arg Pro His Pro Gln His		Ser Gln Gln Pro Pro Pro	
500		505	510
Pro Gln Gln Glu Arg Ser Lys Pro Ser		Phe His Ala Pro Glu Pro	
515		520	525
Lys Ala His Tyr Glu Pro Ala Asp Arg		Ala Arg Glu Val Pro Val	
530		535	540
Arg Thr Thr Ser Arg Ser Pro Val Leu		Ser Arg Arg Asp Ser Pro	
545		550	555
Leu Gln Gly Ser Gly Gln Gln Asn Ser		Gln Ala Gly Gln Arg Asn	
560		565	570
Ser Thr Ser Ile Glu Pro Arg Leu Leu		Trp Glu Arg Val Glu Lys	
575		580	585
Leu Val Pro Arg Pro Gly Ser Gly Ser		Ser Ser Gly Ser Ser Asn	
590		595	600
Ser Gly Ser Gln Pro Gly Ser His Pro		Gly Ser Gln Ser Gly Ser	
605		610	615
Gly Glu Arg Phe Arg Val Arg Ser Ser		Ser Lys Ser Glu Gly Ser	
620		625	630
Pro Ser Gln Arg Leu Glu Asn Ala Val		Lys Lys Pro Glu Asp Lys	
635		640	645
Lys Glu Val Phe Arg Pro Leu Lys Pro		Ala Asp Leu Thr Ala Leu	
650		655	660
Ala Lys Glu Leu Arg Ala Val Glu Asp		Val Arg Pro Pro His Lys	
665		670	675
Val Thr Asp Tyr Ser Ser Ser Ser Glu		Glu Ser Gly Thr Thr Asp	
680		685	690
Glu Glu Asp Asp Asp Val Glu Gln Glu		Gly Ala Asp Glu Ser Thr	
695		700	705
Ser Gly Pro Glu Asp Thr Arg Ala Ala		Ser Ser Leu Asn Leu Ser	
710		715	720
Asn Gly Glu Thr Glu Ser Val Lys Thr		Met Ile Val His Asp Asp	
725		730	735
Val Glu Ser Glu Pro Ala Met Thr Pro		Ser Lys Glu Gly Thr Leu	
740		745	750
Ile Val Arg Gln Thr Gln Ser Ala Ser		Ser Thr Leu Gln Lys His	
755		760	765
Lys Ser Ser Ser Ser Phe Thr Pro Phe		Ile Asp Pro Arg Leu Leu	

	770		775		780
Gln Ile Ser Pro	Ser Ser Gly Thr Thr Val Thr Ser Val Val Gly				
	785		790		795
Phe Ser Cys Asp	Gly Met Arg Pro Glu Ala Ile Arg Gln Asp Pro				
	800		805		810
Thr Arg Lys Gly	Ser Val Val Asn Val Asn Pro Thr Asn Thr Arg				
	815		820		825
Pro Gln Ser Asp	Thr Pro Glu Ile Arg Lys Tyr Lys Lys Arg Phe				
	830		835		840
Asn Ser Glu Ile	Leu Cys Ala Ala Leu Trp Gly Val Asn Leu Leu				
	845		850		855
Val Gly Thr Glu	Ser Gly Leu Met Leu Leu Asp Arg Ser Gly Gln				
	860		865		870
Gly Lys Val Tyr	Pro Leu Ile Asn Arg Arg Arg Phe Gln Gln Met				
	875		880		885
Asp Val Leu Glu	Gly Leu Asn Val Leu Val Thr Ile Ser Gly Lys				
	890		895		900
Lys Asp Lys Leu	Arg Val Tyr Tyr Leu Ser Trp Leu Arg Asn Lys				
	905		910		915
Ile Leu His Asn	Asp Pro Glu Val Glu Lys Lys Gln Gly Trp Thr				
	920		925		930
Thr Val Gly Asp	Leu Glu Gly Cys Val His Tyr Lys Val Val Lys				
	935		940		945
Tyr Glu Arg Ile	Lys Phe Leu Val Ile Ala Leu Lys Ser Ser Val				
	950		955		960
Glu Val Tyr Ala	Trp Ala Pro Lys Pro Tyr His Lys Phe Met Ala				
	965		970		975
Phe Lys Ser Phe	Gly Glu Leu Val His Gly Ser Cys Ala Gly Phe				
	980		985		990
His Ala Val Asp	Val Asp Ser Gly Ser Val Tyr Asp Ile Tyr Leu				
	995		1000		1005
Pro Thr His Ile	Gln Cys Ser Ile Lys Pro His Ala Ile Ile Ile				
	1010		1015		1020
Leu Pro Asn Thr	Asp Gly Met Glu Leu Leu Val Cys Tyr Glu Asp				
	1025		1030		1035
Glu Gly Val Tyr	Val Asn Thr Tyr Gly Arg Ile Thr Lys Asp Val				
	1040		1045		1050
Val Leu Gln Trp	Gly Glu Met Pro Thr Ser Val Ala Tyr Ile Arg				
	1055		1060		1065
Ser Asn Gln Thr	Met Gly Trp Gly Glu Lys Ala Ile Glu Ile Arg				
	1070		1075		1080
Ser Val Glu Thr	Gly His Leu Asp Gly Val Phe Met His Lys Arg				
	1085		1090		1095
Ala Gln Arg Leu	Lys Phe Leu Cys Glu Arg Asn Asp Lys Val Phe				
	1100		1105		1110
Phe Ala Ser Val	Arg Ser Gly Gly Ser Ser Gln Val Tyr Phe Met				
	1115		1120		1125
Thr Leu Gly Arg	Thr Ser Leu Leu Ser Trp				
	1130		1135		

<210> 17

<211> 228

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone Number: 209854

<400> 17

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Met Pro Thr Asn Cys Ala Ala Ala Gly Cys Ala Thr Thr Tyr Asn
 1           5           10           15
Lys His Ile Asn Ile Ser Phe His Arg Phe Pro Leu Asp Pro Lys
          20           25           30
Arg Arg Lys Glu Trp Val Arg Leu Val Arg Arg Lys Asn Phe Val
          35           40           45
Pro Gly Lys His Thr Phe Leu Cys Ser Lys His Phe Glu Ala Ser
          50           55           60
Cys Phe Asp Leu Thr Gly Gln Thr Arg Arg Leu Lys Met Asp Ala
          65           70           75
Val Pro Thr Ile Phe Asp Phe Cys Thr His Ile Lys Ser Met Lys
          80           85           90
Leu Lys Ser Arg Asn Leu Leu Lys Lys Asn Asn Ser Cys Ser Pro
          95          100          105
Ala Gly Pro Ser Asn Leu Lys Ser Asn Ile Ser Ser Gln Gln Val
          110          115          120
Leu Leu Glu His Ser Tyr Ala Phe Arg Asn Pro Met Glu Ala Lys
          125          130          135
Lys Arg Ile Ile Lys Leu Glu Lys Glu Ile Ala Ser Leu Arg Arg
          140          145          150
Lys Met Lys Thr Cys Leu Gln Lys Glu Arg Arg Ala Thr Arg Arg
          155          160          165
Trp Ile Lys Ala Thr Cys Leu Val Lys Asn Leu Glu Ala Asn Ser
          170          175          180
Val Leu Pro Lys Gly Thr Ser Glu His Met Leu Pro Thr Ala Leu
          185          190          195
Ser Ser Leu Pro Leu Glu Asp Phe Lys Ile Leu Glu Gln Asp Gln
          200          205          210
Gln Asp Lys Thr Leu Leu Ser Leu Asn Leu Lys Gln Thr Lys Ser
          215          220          225
Thr Phe Ile

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<210> 18

<211> 503

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone Number: 1384286

<400> 18

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Met Ala Thr Thr Val Thr Cys Thr Arg Phe Thr Asp Glu Tyr Gln
 1           5           10           15
Leu Tyr Glu Asp Ile Gly Lys Gly Ala Phe Ser Val Val Arg Arg
          20           25           30
Cys Val Lys Leu Cys Thr Gly His Glu Tyr Ala Ala Lys Ile Ile
          35           40           45
Asn Thr Lys Lys Leu Ser Ala Arg Asp His Gln Lys Leu Glu Arg

```

50	55	60
Glu Ala Arg Ile Cys Arg Leu Leu Lys His Ser Asn Ile Val Arg		
65	70	75
Leu His Asp Ser Ile Ser Glu Glu Gly Phe His Tyr Leu Val Phe		
80	85	90
Asp Leu Val Thr Gly Gly Glu Leu Phe Glu Asp Ile Val Ala Arg		
95	100	105
Glu Tyr Tyr Ser Glu Ala Asp Ala Ser His Cys Ile Gln Gln Ile		
110	115	120
Leu Glu Ala Val Leu His Cys His Gln Met Gly Val Val His Arg		
125	130	135
Asp Leu Lys Pro Glu Asn Leu Leu Leu Ala Ser Lys Cys Lys Gly		
140	145	150
Ala Ala Val Lys Leu Ala Asp Phe Gly Leu Ala Ile Glu Val Gln		
155	160	165
Gly Asp Gln Gln Ala Trp Phe Gly Phe Ala Gly Thr Pro Gly Tyr		
170	175	180
Leu Ser Pro Glu Val Leu Arg Lys Glu Ala Tyr Gly Lys Pro Val		
185	190	195
Asp Ile Trp Ala Cys Gly Val Ile Leu Tyr Ile Leu Leu Val Gly		
200	205	210
Tyr Pro Pro Phe Trp Asp Glu Asp Gln His Lys Leu Tyr Gln Gln		
215	220	225
Ile Lys Ala Gly Ala Tyr Asp Phe Pro Ser Pro Glu Trp Asp Thr		
230	235	240
Val Thr Pro Glu Ala Lys Asn Leu Ile Asn Gln Met Leu Thr Ile		
245	250	255
Asn Pro Ala Lys Arg Ile Thr Ala His Glu Ala Leu Lys His Pro		
260	265	270
Trp Val Cys Gln Arg Ser Thr Val Ala Ser Met Met His Arg Gln		
275	280	285
Glu Thr Val Glu Cys Leu Lys Lys Phe Asn Ala Arg Arg Lys Leu		
290	295	300
Lys Gly Ala Ile Leu Thr Thr Met Leu Ala Thr Arg Asn Phe Ser		
305	310	315
Ala Ala Lys Ser Leu Leu Asn Lys Lys Ala Asp Gly Val Lys Pro		
320	325	330
His Thr Asn Ser Thr Lys Asn Ser Ala Ala Ala Thr Ser Pro Lys		
335	340	345
Gly Thr Leu Pro Pro Ala Ala Leu Glu Ser Ser Asp Ser Ala Asn		
350	355	360
Thr Thr Ile Glu Asp Glu Asp Ala Lys Ala Arg Lys Gln Glu Ile		
365	370	375
Ile Lys Thr Thr Glu Gln Leu Ile Glu Ala Val Asn Asn Gly Asp		
380	385	390
Phe Glu Ala Tyr Ala Lys Ile Cys Asp Pro Gly Leu Thr Ser Phe		
395	400	405
Glu Pro Glu Ala Leu Gly Asn Leu Val Glu Gly Met Asp Phe His		
410	415	420
Arg Phe Tyr Phe Glu Asn Leu Leu Ala Lys Asn Ser Lys Pro Ile		
425	430	435
His Thr Thr Ile Leu Asn Pro His Val His Val Ile Gly Glu Asp		
440	445	450
Ala Ala Cys Ile Ala Tyr Ile Arg Leu Thr Gln Tyr Ile Asp Gly		
455	460	465
Gln Gly Arg Pro Arg Thr Ser Gln Ser Glu Glu Thr Arg Val Trp		

	470		475		480
His Arg Arg Asp Gly Lys Trp Gln Asn Val His Phe His Cys Ser					
	485		490		495
Gly Ala Pro Val Ala Pro Leu Gln					
	500				

<210> 19
 <211> 433
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte Clone Number: 1512656

<400> 19
 Met Thr Gly Glu Ala Gln Ala Gly Arg Lys Arg Ser Arg Ala Arg
 1 5 10 15
 Pro Glu Gly Thr Glu Pro Val Arg Arg Glu Arg Thr Gln Pro Gly
 20 25 30
 Leu Gly Pro Gly Arg Ala Arg Ala Met Ala Ala Glu Ala Thr Ala
 35 40 45
 Val Ala Gly Ser Gly Ala Val Gly Gly Cys Leu Ala Lys Asp Gly
 50 55 60
 Leu Gln Gln Ser Lys Cys Pro Asp Thr Thr Pro Lys Arg Arg Arg
 65 70 75
 Ala Ser Ser Leu Ser Arg Asp Ala Glu Arg Arg Ala Tyr Gln Trp
 80 85 90
 Cys Arg Glu Tyr Leu Gly Gly Ala Trp Arg Arg Val Gln Pro Glu
 95 100 105
 Glu Leu Arg Val Tyr Pro Val Ser Gly Gly Leu Ser Asn Leu Leu
 110 115 120
 Phe Arg Cys Ser Leu Pro Asp His Leu Pro Ser Val Gly Glu Glu
 125 130 135
 Pro Arg Glu Val Leu Leu Arg Leu Tyr Gly Ala Ile Leu Gln Gly
 140 145 150
 Val Asp Ser Leu Val Leu Glu Ser Val Met Phe Ala Ile Leu Ala
 155 160 165
 Glu Arg Ser Leu Gly Pro Gln Leu Tyr Gly Val Phe Pro Glu Gly
 170 175 180
 Arg Leu Glu Gln Tyr Ile Pro Ser Arg Pro Leu Lys Thr Gln Glu
 185 190 195
 Leu Arg Glu Pro Val Leu Ser Ala Ala Ile Ala Thr Lys Met Ala
 200 205 210
 Gln Phe His Gly Met Glu Met Pro Phe Thr Lys Glu Pro His Trp
 215 220 225
 Leu Phe Gly Thr Met Glu Arg Tyr Leu Lys Gln Ile Gln Asp Leu
 230 235 240
 Pro Pro Thr Gly Leu Pro Glu Met Asn Leu Leu Glu Met Tyr Ser
 245 250 255
 Leu Lys Asp Glu Met Gly Asn Leu Arg Lys Leu Leu Glu Ser Thr
 260 265 270
 Pro Ser Pro Val Val Phe Cys His Asn Asp Ile Gln Glu Gly Asn

275	280	285
Ile Leu Leu Leu Ser Glu Pro Glu Asn Ala Asp Ser Leu Met Leu		
290	295	300
Val Asp Phe Glu Tyr Ser Ser Tyr Asn Tyr Arg Gly Phe Asp Ile		
305	310	315
Gly Asn His Phe Cys Glu Trp Val Tyr Asp Tyr Thr His Glu Glu		
320	325	330
Trp Pro Phe Tyr Lys Ala Arg Pro Thr Asp Tyr Pro Thr Gln Glu		
335	340	345
Gln Gln Leu His Phe Ile Arg His Tyr Leu Ala Glu Ala Lys Lys		
350	355	360
Gly Glu Thr Leu Ser Gln Glu Glu Gln Arg Lys Leu Glu Glu Asp		
365	370	375
Leu Leu Val Glu Val Ser Arg Tyr Ala Leu Ala Ser His Phe Phe		
380	385	390
Trp Gly Leu Trp Ser Ile Leu Gln Ala Ser Met Ser Thr Ile Glu		
395	400	405
Phe Gly Tyr Leu Asp Tyr Ala Gln Ser Arg Phe Gln Phe Tyr Phe		
410	415	420
Gln Gln Lys Gly Gln Leu Thr Ser Val His Ser Ser Ser		
425	430	

<210> 20

<211> 527

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone Number: 2098635

<400> 20

Met Ser Leu Cys Gly Ala Arg Ala Asn Ala Lys Met Met Ala Ala		
1	5	10
Tyr Asn Gly Gly Thr Ser Ala Ala Ala Ala Gly His His His His		
20	25	30
His His His His Leu Pro His Leu Pro Pro Pro His Leu Leu His		
35	40	45
His His His Pro Gln His His Leu His Pro Gly Ser Ala Ala Ala		
50	55	60
Val His Pro Val Gln Gln His Thr Ser Ser Ala Ala Ala Ala Ala		
65	70	75
Ala Ala Ala Ala Ala Ala Ala Ala Met Leu Asn Pro Gly Gln Gln		
80	85	90
Gln Pro Tyr Phe Pro Ser Pro Ala Pro Gly Gln Ala Pro Gly Pro		
95	100	105
Ala Ala Ala Ala Pro Ala Gln Val Gln Ala Ala Ala Ala Ala Thr		
110	115	120
Val Lys Ala His His His Gln His Ser His His Pro Gln Gln Gln		
125	130	135
Leu Asp Ile Glu Pro Asp Arg Pro Ile Gly Tyr Gly Ala Phe Gly		
140	145	150
Val Val Trp Ser Val Thr Asp Pro Arg Asp Gly Lys Arg Val Ala		
155	160	165
Leu Lys Lys Met Pro Asn Val Phe Gln Asn Leu Val Ser Cys Lys		

Arg Val Phe Arg	170	175	180
Glu Leu Lys Met Leu Cys Phe Phe Lys His Asp			
185	190	195	
Asn Val Leu Ser Ala Leu Asp Ile Leu Gln Pro Pro His Ile Asp			
200	205	210	
Tyr Phe Glu Glu Ile Tyr Val Val Thr Glu Leu Met Gln Ser Asp			
215	220	225	
Leu His Lys Ile Ile Val Ser Pro Gln Pro Leu Ser Ser Asp His			
230	235	240	
Val Lys Val Phe Leu Tyr Gln Ile Leu Arg Gly Leu Lys Tyr Leu			
245	250	255	
His Ser Ala Gly Ile Leu His Arg Asp Ile Lys Pro Gly Asn Leu			
260	265	270	
Leu Val Asn Ser Asn Cys Val Leu Lys Ile Cys Asp Phe Gly Leu			
275	280	285	
Ala Arg Val Glu Glu Leu Asp Glu Ser Arg His Met Thr Gln Glu			
290	295	300	
Val Val Thr Gln Tyr Tyr Arg Ala Pro Glu Ile Leu Met Gly Ser			
305	310	315	
Arg His Tyr Ser Asn Ala Ile Asp Ile Trp Ser Val Gly Cys Ile			
320	325	330	
Phe Ala Glu Leu Leu Gly Arg Arg Ile Leu Phe Gln Ala Gln Ser			
335	340	345	
Pro Ile Gln Gln Leu Asp Leu Ile Thr Asp Leu Leu Gly Thr Pro			
350	355	360	
Ser Leu Glu Ala Met Arg Thr Ala Cys Glu Gly Ala Lys Ala His			
365	370	375	
Ile Leu Arg Gly Pro His Lys Gln Pro Ser Leu Pro Val Leu Tyr			
380	385	390	
Thr Leu Ser Ser Gln Ala Thr His Glu Ala Val His Leu Leu Cys			
395	400	405	
Arg Met Leu Val Phe Asp Pro Ser Lys Arg Ile Ser Ala Lys Asp			
410	415	420	
Ala Leu Ala His Pro Tyr Leu Asp Glu Gly Arg Leu Arg Tyr His			
425	430	435	
Thr Cys Met Cys Lys Cys Cys Phe Ser Thr Ser Thr Gly Arg Val			
440	445	450	
Tyr Thr Ser Asp Phe Glu Pro Val Thr Asn Pro Lys Phe Asp Asp			
455	460	465	
Thr Phe Glu Lys Asn Leu Ser Ser Val Arg Gln Val Lys Glu Ile			
470	475	480	
Ile His Gln Phe Ile Leu Glu Gln Gln Lys Gly Asn Arg Val Pro			
485	490	495	
Leu Cys Ile Asn Pro Gln Ser Ala Ala Phe Lys Ser Phe Ile Ser			
500	505	510	
Ser Thr Val Ala Gln Pro Ser Glu Met Pro Pro Ser Pro Leu Val			
515	520	525	
Trp Glu			

<210> 21
 <211> 322
 <212> PRT
 <213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone Number: 2446646

<400> 21

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Met Glu Gly Ile Ser Asn Phe Lys Thr Pro Ser Lys Leu Ser Glu
  1           5           10           15
Lys Lys Lys Ser Val Leu Cys Ser Thr Pro Thr Ile Asn Ile Pro
          20           25           30
Ala Ser Pro Phe Met Gln Lys Leu Gly Phe Gly Thr Gly Val Asn
          35           40           45
Val Tyr Leu Met Lys Arg Ser Pro Arg Gly Leu Ser His Ser Pro
          50           55           60
Trp Ala Val Lys Lys Ile Asn Pro Ile Cys Asn Asp His Tyr Arg
          65           70           75
Ser Val Tyr Gln Lys Arg Leu Met Asp Glu Ala Lys Ile Leu Lys
          80           85           90
Ser Leu His His Pro Asn Ile Val Gly Tyr Arg Ala Phe Thr Glu
          95          100          105
Ala Asn Asp Gly Ser Leu Cys Leu Ala Met Glu Tyr Gly Gly Glu
          110         115         120
Lys Ser Leu Asn Asp Leu Ile Glu Glu Arg Tyr Lys Ala Ser Gln
          125         130         135
Asp Pro Phe Pro Ala Ala Ile Ile Leu Lys Val Ala Leu Asn Met
          140         145         150
Ala Arg Gly Leu Lys Tyr Leu His Gln Glu Lys Lys Leu Leu His
          155         160         165
Gly Asp Ile Lys Ser Ser Asn Val Val Ile Lys Gly Asp Phe Glu
          170         175         180
Thr Ile Lys Ile Cys Asp Val Gly Val Ser Leu Pro Leu Asp Glu
          185         190         195
Asn Met Thr Val Thr Asp Pro Glu Ala Cys Tyr Ile Gly Thr Glu
          200         205         210
Pro Trp Lys Pro Lys Glu Ala Val Glu Glu Asn Gly Val Ile Thr
          215         220         225
Asp Lys Ala Asp Ile Phe Ala Phe Gly Leu Thr Leu Trp Glu Met
          230         235         240
Met Thr Leu Ser Ile Pro His Ile Asn Leu Ser Asn Asp Asp Asp
          245         250         255
Asp Glu Asp Lys Thr Phe Asp Glu Ser Asp Phe Asp Asp Glu Ala
          260         265         270
Tyr Tyr Ala Ala Leu Gly Thr Arg Pro Pro Ile Asn Met Glu Glu
          275         280         285
Leu Asp Glu Ser Tyr Gln Lys Val Ile Glu Leu Phe Ser Val Cys
          290         295         300
Thr Asn Glu Asp Pro Lys Asp Arg Pro Ser Ala Ala His Ile Val
          305         310         315
Glu Ala Leu Glu Thr Asp Val
          320

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<210> 22

<211> 802

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone Number: 2764911

<400> 22

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Met Glu Glu Glu Gly Gly Ser Ser Gly Gly Ala Ala Gly Thr Ser
  1           5           10           15
Ala Asp Gly Gly Asp Gly Gly Glu Gln Leu Leu Thr Val Lys His
          20           25           30
Glu Leu Arg Thr Ala Asn Leu Thr Gly His Ala Glu Lys Val Gly
          35           40           45
Ile Glu Asn Phe Glu Leu Leu Lys Val Leu Gly Thr Gly Ala Tyr
          50           55           60
Gly Lys Val Phe Leu Val Arg Lys Ile Ser Gly His Asp Thr Gly
          65           70           75
Lys Leu Tyr Ala Met Lys Val Leu Lys Lys Ala Thr Ile Val Gln
          80           85           90
Lys Ala Lys Thr Thr Glu His Thr Arg Thr Glu Arg Gln Val Leu
          95          100          105
Glu His Ile Arg Gln Ser Pro Phe Leu Val Thr Leu His Tyr Ala
          110          115          120
Phe Gln Thr Glu Thr Lys Leu His Leu Ile Leu Asp Tyr Ile Asn
          125          130          135
Gly Gly Glu Leu Phe Thr His Leu Ser Gln Arg Glu Arg Phe Thr
          140          145          150
Glu His Glu Val Gln Ile Tyr Val Gly Glu Ile Val Leu Ala Leu
          155          160          165
Glu His Leu His Lys Leu Gly Ile Ile Tyr Arg Asp Ile Lys Leu
          170          175          180
Glu Asn Ile Leu Leu Asp Ser Asn Gly His Val Val Leu Thr Asp
          185          190          195
Phe Gly Leu Ser Lys Glu Phe Val Ala Asp Glu Thr Glu Arg Ala
          200          205          210
Tyr Ser Phe Cys Gly Thr Ile Glu Tyr Met Ala Pro Asp Ile Val
          215          220          225
Arg Gly Gly Asp Ser Gly His Asp Lys Ala Val Asp Trp Trp Ser
          230          235          240
Leu Gly Val Leu Met Tyr Glu Leu Leu Thr Gly Ala Ser Pro Phe
          245          250          255
Thr Val Asp Gly Glu Lys Asn Ser Gln Ala Glu Ile Ser Arg Arg
          260          265          270
Ile Leu Lys Ser Glu Pro Pro Tyr Pro Gln Glu Met Ser Ala Leu
          275          280          285
Ala Lys Asp Leu Ile Gln Arg Leu Leu Met Lys Asp Pro Lys Lys
          290          295          300
Arg Leu Gly Cys Gly Pro Arg Asp Ala Asp Glu Ile Lys Glu His
          305          310          315
Leu Phe Phe Gln Lys Ile Asn Trp Asp Asp Leu Ala Ala Lys Lys
          320          325          330
Val Pro Ala Pro Phe Lys Pro Val Ile Arg Asp Glu Leu Asp Val
          335          340          345
Ser Asn Phe Ala Glu Glu Phe Thr Glu Met Asp Pro Thr Tyr Ser
          350          355          360
Pro Ala Ala Leu Pro Gln Ser Ser Glu Lys Leu Phe Gln Gly Tyr
          365          370          375
Ser Phe Val Ala Pro Ser Ile Leu Phe Lys Arg Asn Ala Ala Val
          380          385          390
Ile Asp Pro Leu Gln Phe His Met Gly Val Glu Arg Pro Gly Val

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	395		400		405
Thr Asn Val Ala Arg Ser Ala Met Met Lys Asp Ser Pro Phe Tyr					
	410		415		420
Gln His Tyr Asp Leu Asp Leu Lys Asp Lys Pro Leu Gly Glu Gly					
	425		430		435
Ser Phe Ser Ile Cys Arg Lys Cys Val His Lys Lys Ser Asn Gln					
	440		445		450
Ala Phe Ala Val Lys Ile Ile Ser Lys Arg Met Glu Ala Asn Thr					
	455		460		465
Gln Lys Glu Ile Thr Ala Leu Glu Leu Cys Glu Gly His Pro Asn					
	470		475		480
Ile Val Lys Leu His Glu Val Phe His Asp Gln Leu His Thr Phe					
	485		490		495
Leu Val Met Glu Leu Leu Asn Gly Gly Glu Leu Phe Glu Arg Ile					
	500		505		510
Lys Lys Lys Lys His Phe Ser Glu Thr Glu Ala Ser Tyr Ile Met					
	515		520		525
Arg Lys Leu Val Ser Ala Val Ser His Met His Asp Val Gly Val					
	530		535		540
Val His Arg Asp Leu Lys Pro Glu Asn Leu Leu Phe Thr Asp Glu					
	545		550		555
Asn Asp Asn Leu Glu Ile Lys Ile Ile Asp Phe Gly Phe Ala Arg					
	560		565		570
Leu Lys Pro Pro Asp Asn Gln Pro Leu Lys Thr Pro Cys Phe Thr					
	575		580		585
Leu His Tyr Ala Ala Pro Glu Leu Leu Asn Gln Asn Gly Tyr Asp					
	590		595		600
Glu Ser Cys Asp Leu Trp Ser Leu Gly Val Ile Leu Tyr Thr Met					
	605		610		615
Leu Ser Gly Gln Val Pro Phe Gln Ser His Asp Arg Ser Leu Thr					
	620		625		630
Cys Thr Ser Ala Val Glu Ile Met Lys Lys Ile Lys Lys Gly Asp					
	635		640		645
Phe Ser Phe Glu Gly Glu Ala Trp Lys Asn Val Ser Gln Glu Ala					
	650		655		660
Lys Asp Leu Ile Gln Gly Leu Leu Thr Val Asp Pro Asn Lys Arg					
	665		670		675
Leu Lys Met Ser Gly Leu Arg Tyr Asn Glu Trp Leu Gln Asp Gly					
	680		685		690
Ser Gln Leu Ser Ser Asn Pro Leu Met Thr Pro Asp Ile Leu Gly					
	695		700		705
Ser Ser Gly Ala Ala Val His Thr Cys Val Lys Ala Thr Phe His					
	710		715		720
Ala Phe Asn Lys Tyr Lys Arg Glu Gly Phe Cys Leu Gln Asn Val					
	725		730		735
Asp Lys Ala Pro Leu Ala Lys Arg Arg Lys Met Lys Lys Thr Ser					
	740		745		750
Thr Ser Thr Glu Thr Arg Ser Ser Ser Ser Glu Ser Ser His Ser					
	755		760		765
Ser Ser Ser His Ser His Gly Lys Thr Thr Pro Thr Lys Thr Leu					
	770		775		780
Gln Pro Ser Asn Pro Ala Asp Ser Asn Asn Pro Glu Thr Leu Phe					
	785		790		795
Gln Phe Ser Asp Ser Val Ala					
	800				

<210> 23
 <211> 641
 <212> PRT
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte Clone Number: 3013946

<400> 23
 Met Ala Thr Thr Val Thr Cys Thr Arg Phe Thr Asp Glu Tyr Gln
 1 5 10 15
 Leu Tyr Glu Asp Ile Gly Lys Gly Ala Phe Ser Val Val Arg Arg
 20 25 30
 Cys Val Lys Leu Cys Thr Gly His Glu Tyr Ala Ala Lys Ile Ile
 35 40 45
 Asn Thr Lys Lys Leu Ser Ala Arg Asp His Gln Lys Leu Glu Arg
 50 55 60
 Glu Ala Arg Ile Cys Arg Leu Leu Lys His Ser Asn Ile Val Arg
 65 70 75
 Leu His Asp Ser Ile Ser Glu Glu Gly Phe His Tyr Leu Val Phe
 80 85 90
 Asp Leu Val Thr Gly Gly Glu Leu Phe Glu Asp Ile Val Ala Arg
 95 100 105
 Glu Tyr Tyr Ser Glu Ala Asp Ala Ser His Cys Ile Gln Gln Ile
 110 115 120
 Leu Glu Ala Val Leu His Cys His Gln Met Gly Val Val His Arg
 125 130 135
 Asp Leu Lys Pro Glu Asn Leu Leu Leu Ala Ser Lys Cys Lys Gly
 140 145 150
 Ala Ala Val Lys Leu Ala Asp Phe Gly Leu Ala Ile Glu Val Gln
 155 160 165
 Gly Asp Gln Gln Ala Trp Phe Gly Phe Ala Gly Thr Pro Gly Tyr
 170 175 180
 Leu Ser Pro Glu Val Leu Arg Lys Glu Ala Tyr Gly Lys Pro Val
 185 190 195
 Asp Ile Trp Ala Cys Gly Val Ile Leu Tyr Ile Leu Leu Val Gly
 200 205 210
 Tyr Pro Pro Phe Trp Asp Glu Asp Gln His Lys Leu Tyr Gln Gln
 215 220 225
 Ile Lys Ala Gly Ala Tyr Asp Phe Pro Ser Pro Glu Trp Asp Thr
 230 235 240
 Val Thr Pro Glu Ala Lys Asn Leu Ile Asn Gln Met Leu Thr Ile
 245 250 255
 Asn Pro Ala Lys Arg Ile Thr Ala His Glu Ala Leu Lys His Pro
 260 265 270
 Trp Val Cys Gln Arg Ser Thr Val Ala Ser Met Met His Arg Gln
 275 280 285
 Glu Thr Val Glu Cys Leu Lys Lys Phe Asn Ala Arg Arg Lys Leu
 290 295 300
 Lys Gly Ala Ile Leu Thr Thr Met Leu Ala Thr Arg Asn Phe Ser
 305 310 315
 Ala Lys Ser Leu Leu Asn Lys Lys Ala Asp Gly Val Lys Pro Gln
 320 325 330
 Thr Asn Ser Thr Lys Asn Ser Ala Ala Ala Thr Ser Pro Lys Gly
 335 340 345

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Thr Leu Pro Pro Ala Ala Leu Glu Pro Gln Thr Thr Val Ile His
350                               355                               360
Asn Pro Val Asp Gly Ile Lys Glu Ser Ser Asp Ser Ala Asn Thr
365                               370                               375
Thr Ile Glu Asp Glu Asp Ala Lys Ala Pro Arg Val Pro Asp Ile
380                               385                               390
Leu Ser Ser Val Arg Arg Gly Ser Gly Ala Pro Glu Ala Glu Gly
395                               400                               405
Pro Leu Pro Cys Pro Ser Pro Ala Pro Phe Gly Pro Leu Pro Ala
410                               415                               420
Pro Ser Pro Arg Ile Ser Asp Ile Leu Asn Ser Val Arg Arg Gly
425                               430                               435
Ser Gly Thr Pro Glu Ala Glu Gly Pro Leu Ser Ala Gly Pro Pro
440                               445                               450
Pro Cys Leu Ser Pro Ala Leu Leu Gly Pro Leu Ser Ser Pro Ser
455                               460                               465
Pro Arg Ile Ser Asp Ile Leu Asn Ser Val Arg Arg Gly Ser Gly
470                               475                               480
Thr Pro Glu Ala Lys Gly Pro Ser Pro Val Gly Pro Pro Pro Cys
485                               490                               495
Pro Ser Pro Thr Ile Pro Gly Pro Leu Pro Thr Pro Ser Arg Lys
500                               505                               510
Gln Glu Ile Ile Lys Thr Thr Glu Gln Leu Ile Glu Ala Val Asn
515                               520                               525
Asn Gly Asp Phe Glu Ala Tyr Ala Lys Ile Cys Asp Pro Gly Leu
530                               535                               540
Thr Ser Phe Glu Pro Glu Ala Leu Gly Asn Leu Val Glu Gly Met
545                               550                               555
Asp Phe His Arg Phe Tyr Phe Glu Asn Leu Leu Ala Lys Asn Ser
560                               565                               570
Lys Pro Ile His Thr Thr Ile Leu Asn Pro His Val His Val Ile
575                               580                               585
Gly Glu Asp Ala Ala Cys Ile Ala Tyr Ile Arg Leu Thr Gln Tyr
590                               595                               600
Ile Asp Gly Gln Gly Arg Pro Arg Thr Ser Gln Ser Glu Glu Thr
605                               610                               615
Arg Val Trp His Arg Arg Asp Gly Lys Trp Gln Asn Val His Phe
620                               625                               630
His Cys Ser Gly Ala Pro Val Ala Pro Leu Gln
635                               640

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<210> 24

<211> 588

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone Number: 067967

<400> 24

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Met Gly Gly Thr Ala Arg Gly Pro Gly Arg Lys Asp Ala Gly Pro
1           5           10          15
Pro Gly Ala Gly Leu Pro Pro Gln Gln Arg Arg Leu Gly Asp Gly
20          25          30
Val Tyr Asp Thr Phe Met Met Ile Asp Glu Thr Lys Cys Pro Pro

```

	35		40		45
Cys Ser Asn Val	Leu Cys Asn Pro Ser	Glu Pro Pro Ser Pro Arg			
	50		55		60
Arg Leu Asn Met	Thr Thr Glu Gln Phe Thr	Gly Asp His Thr Gln			
	65		70		75
His Phe Leu Asp	Gly Gly Glu Met Lys Val	Glu Gln Leu Phe Gln			
	80		85		90
Glu Phe Gly Asn	Arg Lys Ser Asn Thr Ile	Gln Ser Asp Gly Ile			
	95		100		105
Ser Asp Ser Glu	Lys Cys Ser Pro Thr Val	Ser Gln Gly Lys Ser			
	110		115		120
Ser Asp Cys Leu	Asn Thr Val Lys Ser Asn	Ser Ser Ser Lys Ala			
	125		130		135
Pro Lys Val Val	Pro Leu Thr Pro Glu Gln	Ala Leu Lys Gln Tyr			
	140		145		150
Lys His His Leu	Thr Ala Tyr Glu Lys Leu	Glu Ile Ile Asn Tyr			
	155		160		165
Pro Glu Ile Tyr	Phe Val Gly Pro Asn Ala	Lys Lys Arg His Gly			
	170		175		180
Val Ile Gly Gly	Pro Asn Asn Gly Gly Tyr	Asp Asp Ala Asp Gly			
	185		190		195
Ala Tyr Ile His	Val Pro Arg Asp His Leu	Ala Tyr Arg Tyr Glu			
	200		205		210
Val Leu Lys Ile	Ile Gly Lys Gly Ser Phe	Gly Gln Val Ala Arg			
	215		220		225
Val Tyr Asp His	Lys Leu Arg Gln Tyr Val	Ala Leu Lys Met Val			
	230		235		240
Arg Asn Glu Lys	Arg Phe His Arg Gln Ala	Ala Glu Glu Ile Arg			
	245		250		255
Ile Leu Glu His	Leu Lys Lys Gln Asp Lys	Thr Gly Ser Met Asn			
	260		265		270
Val Ile His Met	Leu Glu Ser Phe Thr Phe	Arg Asn His Val Cys			
	275		280		285
Met Ala Phe Glu	Leu Leu Ser Ile Asp Leu	Tyr Glu Leu Ile Lys			
	290		295		300
Lys Asn Lys Phe	Gln Gly Phe Ser Val Gln	Leu Val Arg Lys Phe			
	305		310		315
Ala Gln Ser Ile	Leu Gln Ser Leu Asp Ala	Leu His Lys Asn Lys			
	320		325		330
Ile Ile His Cys	Asp Leu Lys Pro Glu Asn	Ile Leu Leu Lys His			
	335		340		345
His Gly Arg Ser	Ser Thr Lys Val Ile Asp	Phe Gly Ser Ser Cys			
	350		355		360
Phe Glu Tyr Gln	Lys Leu Tyr Thr Tyr Ile	Gln Ser Arg Phe Tyr			
	365		370		375
Arg Ala Pro Glu	Ile Ile Leu Gly Ser Arg	Tyr Ser Thr Pro Ile			
	380		385		390
Asp Ile Trp Ser	Phe Gly Cys Ile Leu Ala	Glu Leu Leu Thr Gly			
	395		400		405
Gln Pro Leu Phe	Pro Gly Glu Asp Glu Gly	Asp Gln Leu Ala Cys			
	410		415		420
Met Met Glu Leu	Leu Gly Met Pro Pro Pro	Lys Leu Leu Glu Gln			
	425		430		435
Ser Lys Arg Ala	Lys Tyr Phe Ile Asn Ser	Lys Gly Ile Pro Arg			
	440		445		450
Tyr Cys Ser Val	Thr Thr Gln Ala Asp Gly	Arg Val Val Leu Val			

	455		460		465
Gly Gly Arg Ser	Arg Arg Gly Lys Lys	Arg Gly Pro Pro Gly Ser			
	470		475		480
Lys Asp Trp Gly	Thr Ala Leu Lys Gly	Cys Asp Asp Tyr Leu Phe			
	485		490		495
Ile Glu Phe Leu	Lys Arg Cys Leu His	Trp Asp Pro Ser Ala Arg			
	500		505		510
Leu Thr Pro Ala	Gln Ala Leu Arg His	Pro Trp Ile Ser Lys Ser			
	515		520		525
Val Pro Arg Pro	Leu Thr Thr Ile Asp	Lys Val Ser Gly Lys Arg			
	530		535		540
Val Val Asn Pro	Ala Ser Ala Phe Gln	Gly Leu Gly Ser Lys Leu			
	545		550		555
Pro Pro Val Val	Gly Ile Ala Asn Lys	Leu Lys Ala Asn Leu Met			
	560		565		570
Ser Glu Thr Asn	Gly Ser Ile Pro Leu	Cys Ser Val Leu Pro Lys			
	575		580		585
Leu Ile Ser					

<210> 25

<211> 389

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone Number: 346275

<400> 25

Met Ser Asp Val	Cys Ser Ser Gln Arg	Ala Glu His Glu His Leu
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Pro Gly Leu Val	Pro Pro Pro Ser Gly Met	Gly Val Arg Lys Gly
	20	25 30
Ser Ser Pro Leu	Lys Ser His Pro Cys Arg	Glu Lys Ser Val Ser
	35	40 45
Asn Arg Arg Ser	Gly Lys Thr Ile Val Arg	Ser Ala Val Glu Glu
	50	55 60
Val Arg Thr Ala	Gly Leu Phe Arg Ser Gly	Phe Ser Glu Glu Lys
	65	70 75
Ala Thr Gly Lys	Leu Phe Ala Val Lys Cys	Ile Pro Lys Lys Ala
	80	85 90
Leu Lys Gly Lys	Glu Ser Ser Ile Glu Asn	Glu Ile Ala Val Leu
	95	100 105
Arg Lys Ile Lys	His Glu Asn Ile Val Ala	Leu Glu Asp Ile Tyr
	110	115 120
Glu Ser Pro Asn	His Leu Tyr Leu Val Met	Gln Leu Val Ser Gly
	125	130 135
Gly Glu Leu Phe	Asp Arg Ile Val Glu Lys	Gly Phe Tyr Thr Glu
	140	145 150
Lys Asp Ala Ser	Thr Leu Ile Arg Gln Val	Leu Asp Ala Val Tyr
	155	160 165
Tyr Leu His Arg	Met Gly Ile Val His Arg	Asp Leu Lys Pro Glu
	170	175 180
Asn Leu Leu Tyr	Tyr Ser Gln Asp Glu Glu	Ser Lys Ile Met Ile
	185	190 195

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Ser Asp Phe Gly Leu Ser Lys Met Glu Gly Lys Gly Asp Val Met
      200                      205                      210
Ser Thr Ala Cys Gly Thr Pro Gly Tyr Val Ala Pro Glu Val Leu
      215                      220                      225
Ala Gln Lys Pro Tyr Ser Lys Ala Val Asp Cys Trp Ser Ile Gly
      230                      235                      240
Val Ile Ala Tyr Ile Leu Leu Cys Gly Tyr Pro Pro Phe Tyr Asp
      245                      250                      255
Glu Asn Asp Ser Lys Leu Phe Glu Gln Ile Leu Lys Ala Glu Tyr
      260                      265                      270
Glu Phe Asp Ser Pro Tyr Trp Asp Asp Ile Ser Asp Ser Ala Lys
      275                      280                      285
Asp Phe Ile Arg Asn Leu Met Glu Lys Asp Pro Asn Lys Arg Tyr
      290                      295                      300
Thr Cys Glu Gln Ala Ala Arg His Pro Trp Ile Ala Gly Asp Thr
      305                      310                      315
Ala Leu Asn Lys Asn Ile His Glu Ser Val Ser Ala Gln Ile Arg
      320                      325                      330
Lys Asn Phe Ala Lys Ser Lys Trp Arg Gln Ala Phe Asn Ala Thr
      335                      340                      345
Ala Val Val Arg His Met Arg Lys Leu His Leu Gly Ser Ser Leu
      350                      355                      360
Asp Ser Ser Asn Ala Ser Val Ser Ser Ser Leu Ser Leu Ala Ser
      365                      370                      375
Gln Lys Asp Cys Ala Tyr Val Ala Lys Pro Glu Ser Leu Ser
      380                      385

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<210> 26

<211> 343

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone Number: 283746

<400> 26

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Met Ile Gly Glu Glu Ala Met Ile Asn Tyr Glu Asn Phe Leu Lys
  1                      5                      10                      15
Val Gly Glu Lys Ala Gly Ala Lys Cys Lys Gln Phe Phe Thr Ala
      20                      25                      30
Lys Val Phe Ala Lys Leu Leu His Thr Asp Ser Tyr Gly Arg Ile
      35                      40                      45
Ser Ile Met Gln Phe Phe Asn Tyr Val Met Arg Lys Val Trp Leu
      50                      55                      60
His Gln Thr Arg Ile Gly Leu Ser Leu Tyr Asp Val Ala Gly Gln
      65                      70                      75
Gly Tyr Leu Arg Glu Ser Asp Leu Glu Asn Tyr Ile Leu Glu Leu
      80                      85                      90
Ile Pro Thr Leu Pro Gln Leu Asp Gly Leu Glu Lys Ser Phe Tyr
      95                      100                     105
Ser Phe Tyr Val Cys Thr Ala Val Arg Lys Phe Phe Phe Phe Leu
      110                     115                     120
Asp Pro Leu Arg Thr Gly Lys Ile Lys Ile Gln Asp Ile Leu Ala
      125                     130                     135

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Cys	Ser	Phe	Leu	Asp	Asp	Leu	Leu	Glu	Leu	Arg	Asp	Glu	Glu	Leu	140	145	150
Ser	Lys	Glu	Ser	Gln	Glu	Thr	Asn	Trp	Phe	Ser	Ala	Pro	Ser	Ala	155	160	165
Leu	Arg	Val	Tyr	Gly	Gln	Tyr	Leu	Asn	Leu	Asp	Lys	Asp	His	Asn	170	175	180
Gly	Met	Leu	Ser	Lys	Glu	Glu	Leu	Ser	Arg	Tyr	Gly	Thr	Ala	Thr	185	190	195
Met	Thr	Asn	Val	Phe	Leu	Asp	Arg	Val	Phe	Gln	Glu	Cys	Leu	Thr	200	205	210
Tyr	Asp	Gly	Glu	Met	Asp	Tyr	Lys	Thr	Tyr	Leu	Asp	Phe	Val	Leu	215	220	225
Ala	Leu	Glu	Asn	Arg	Lys	Glu	Pro	Ala	Ala	Leu	Gln	Tyr	Ile	Phe	230	235	240
Lys	Leu	Leu	Asp	Ile	Glu	Asn	Lys	Gly	Tyr	Leu	Asn	Val	Phe	Ser	245	250	255
Leu	Asn	Tyr	Phe	Phe	Arg	Ala	Ile	Gln	Glu	Leu	Met	Lys	Ile	His	260	265	270
Gly	Gln	Asp	Pro	Val	Ser	Phe	Gln	Asp	Val	Lys	Asp	Glu	Ile	Phe	275	280	285
Asp	Met	Val	Lys	Pro	Lys	Asp	Pro	Leu	Lys	Ile	Ser	Leu	Gln	Asp	290	295	300
Leu	Ile	Asn	Ser	Asn	Gln	Gly	Asp	Thr	Val	Thr	Thr	Ile	Leu	Ile	305	310	315
Asp	Leu	Asn	Gly	Phe	Trp	Thr	Tyr	Glu	Asn	Arg	Glu	Ala	Leu	Val	320	325	330
Ala	Asn	Asp	Ser	Glu	Asn	Ser	Ala	Asp	Leu	Asp	Asp	Thr			335	340	

<210> 27

<211> 184

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone Number: 2696537

<400> 27

Met	Gly	Asn	Gly	Met	Asn	Lys	Ile	Leu	Pro	Gly	Leu	Tyr	Ile	Gly	1	5	10	15
Asn	Phe	Lys	Asp	Ala	Arg	Asp	Ala	Glu	Gln	Leu	Ser	Lys	Asn	Lys	20	25	30	
Val	Thr	His	Ile	Leu	Ser	Val	His	Asp	Ser	Ala	Arg	Pro	Met	Leu	35	40	45	
Glu	Gly	Val	Lys	Tyr	Leu	Cys	Ile	Pro	Ala	Ala	Asp	Ser	Pro	Ser	50	55	60	
Gln	Asn	Leu	Thr	Arg	His	Phe	Lys	Glu	Ser	Ile	Lys	Phe	Ile	His	65	70	75	
Glu	Cys	Arg	Leu	Arg	Gly	Glu	Ser	Cys	Leu	Val	His	Cys	Leu	Ala	80	85	90	
Gly	Val	Ser	Arg	Ser	Val	Thr	Leu	Val	Ile	Ala	Tyr	Ile	Met	Thr	95	100	105	
Val	Thr	Asp	Phe	Gly	Trp	Glu	Asp	Ala	Leu	His	Thr	Val	Arg	Ala	110	115	120	

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Gly Arg Ser Cys Ala Asn Pro Asn Val Gly Phe Gln Arg Gln Leu
      125                      130                      135
Gln Glu Phe Glu Lys His Glu Val His Gln Tyr Arg Gln Trp Leu
      140                      145                      150
Lys Glu Glu Tyr Gly Glu Ser Pro Leu Gln Asp Ala Glu Glu Ala
      155                      160                      165
Lys Asn Ile Leu Ala Ala Pro Gly Ile Leu Lys Phe Trp Ala Phe
      170                      175                      180
Leu Arg Arg Leu

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<210> 29
<211> 118
<212> PRT
<213> Homo sapiens

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<220>
<221> misc_feature
<223> Incyte Clone Number: 619292

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<400> 29
Met Gly Leu Ile Asp Gly Met His Thr His Leu Gly Ala Pro Gly
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Leu Tyr Ile Gln Thr Leu Leu Pro Gly Ser Pro Ala Ala Ala Asp
      20           25           30
Gly Arg Leu Ser Leu Gly Asp Arg Ile Leu Glu Val Asn Gly Ser
      35           40           45
Ser Leu Leu Gly Leu Gly Tyr Leu Arg Ala Val Asp Leu Ile Arg
      50           55           60
His Gly Gly Lys Lys Met Arg Phe Leu Val Ala Lys Ser Asp Val
      65           70           75
Gly Lys Gln Pro Arg Arg Ser Ile Ser Ala Arg Pro Leu Ser Arg
      80           85           90
Gly Ala Ala Arg Thr Pro Pro Gln Ala Arg His Pro Val Pro Pro
      95           100          105
Gly Asp Thr Gly Leu Pro Pro Ala Phe Val Pro Val Leu
      110          115

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<210> 30
<211> 356
<212> PRT
<213> Homo sapiens

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<220>
<221> misc_feature
<223> Incyte Clone Number: 2054049

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<400> 30
Met Val Gly Val Ser Gly Lys Arg Ser Lys Glu Asp Glu Lys Tyr
  1           5           10           15
Leu Gln Ala Ile Met Asp Ser Asn Ala Gln Ser His Lys Ile Phe
      20           25           30
Ile Phe Asp Ala Arg Pro Ser Val Asn Ala Val Ala Asn Lys Ala
      35           40           45
Lys Gly Gly Gly Tyr Glu Ser Glu Asp Ala Tyr Gln Asn Ala Glu

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50	55	60
Leu Val Phe Leu Asp Ile His Asn Ile His Val Met Arg Glu Ser		
65	70	75
Leu Arg Lys Leu Lys Glu Ile Val Tyr Pro Asn Ile Glu Glu Thr		
80	85	90
His Trp Leu Ser Asn Leu Glu Ser Thr His Trp Leu Glu His Ile		
95	100	105
Lys Leu Ile Leu Ala Gly Ala Leu Arg Ile Ala Asp Lys Val Glu		
110	115	120
Ser Gly Lys Thr Ser Val Val Val His Cys Ser Asp Gly Trp Asp		
125	130	135
Arg Thr Ala Gln Leu Thr Ser Leu Ala Met Leu Met Leu Asp Gly		
140	145	150
Tyr Tyr Arg Thr Ile Arg Gly Phe Glu Val Leu Val Glu Lys Glu		
155	160	165
Trp Leu Ser Phe Gly His Arg Phe Gln Leu Arg Val Gly His Gly		
170	175	180
Asp Lys Asn His Ala Asp Ala Asp Arg Ser Pro Val Phe Leu Gln		
185	190	195
Phe Ile Asp Cys Val Trp Gln Met Thr Arg Gln Phe Pro Thr Ala		
200	205	210
Phe Glu Phe Asn Glu Tyr Phe Leu Ile Thr Ile Leu Asp His Leu		
215	220	225
Tyr Ser Cys Leu Phe Gly Thr Phe Leu Cys Asn Ser Glu Gln Gln		
230	235	240
Arg Gly Lys Glu Asn Leu Pro Lys Arg Thr Val Ser Leu Trp Ser		
245	250	255
Tyr Ile Asn Ser Gln Leu Glu Asp Phe Thr Asn Pro Leu Tyr Gly		
260	265	270
Ser Tyr Ser Asn His Val Leu Tyr Pro Val Ala Ser Met Arg His		
275	280	285
Leu Glu Leu Trp Val Gly Tyr Tyr Ile Arg Trp Asn Pro Arg Met		
290	295	300
Lys Pro Gln Glu Pro Ile His Asn Arg Tyr Lys Glu Leu Leu Ala		
305	310	315
Lys Arg Ala Glu Leu Gln Lys Lys Val Glu Glu Leu Gln Arg Glu		
320	325	330
Ile Ser Asn Arg Ser Thr Ser Ser Ser Glu Arg Ala Ser Ser Pro		
335	340	345
Ala Gln Cys Val Thr Pro Val Gln Thr Val Val		
350	355	

<210> 31

<211> 453

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone Number: 2843910

<400> 31

Met Ala Gly Ala Gly Gly Phe Gly Cys Pro Ala Gly Gly Asn Asp
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Phe Gln Trp Cys Phe Ser Gln Val Lys Gly Ala Ile Asp Glu Asp

20	25	30
Val Ala Glu Ala Asp Ile Ile Ser Thr	Val Glu Phe Asn Tyr Ser	
35	40	45
Gly Asp Leu Leu Ala Thr Gly Asp Lys	Gly Gly Arg Val Val Ile	
50	55	60
Phe Gln Arg Glu Gln Glu Asn Lys Ser	Arg Pro His Ser Arg Gly	
65	70	75
Glu Tyr Asn Val Tyr Ser Thr Phe Gln	Ser His Glu Pro Glu Phe	
80	85	90
Asp Tyr Leu Lys Ser Leu Glu Ile Glu	Glu Lys Ile Asn Lys Ile	
95	100	105
Arg Trp Leu Pro Gln Gln Asn Ala Ala	His Phe Leu Leu Ser Thr	
110	115	120
Asn Asp Lys Thr Ile Lys Leu Trp Lys	Ile Ser Glu Arg Asp Lys	
125	130	135
Arg Ala Glu Gly Tyr Asn Leu Lys Asp	Glu Asp Gly Arg Leu Arg	
140	145	150
Asp Pro Phe Arg Ile Thr Ala Leu Arg	Val Pro Ile Leu Lys Pro	
155	160	165
Met Asp Leu Met Val Glu Ala Ser Pro	Arg Arg Ile Phe Ala Asn	
170	175	180
Ala His Thr Tyr His Ile Asn Ser Ile	Ser Val Asn Ser Asp His	
185	190	195
Glu Thr Tyr Leu Ser Ala Asp Asp Leu	Arg Ile Asn Leu Trp His	
200	205	210
Leu Glu Ile Thr Asp Arg Ser Phe Asn	Ile Val Asp Ile Lys Pro	
215	220	225
Ala Asn Met Glu Glu Leu Thr Glu Val	Ile Thr Ala Ala Glu Phe	
230	235	240
His Pro His Gln Cys Asn Val Phe Val	Tyr Ser Ser Ser Lys Gly	
245	250	255
Thr Ile Arg Leu Cys Asp Met Arg Ser	Ser Ala Leu Cys Asp Arg	
260	265	270
His Ser Lys Phe Phe Glu Glu Pro Glu	Asp Pro Ser Ser Arg Ser	
275	280	285
Phe Phe Ser Glu Ile Ile Ser Ser Ile	Ser Asp Val Lys Phe Ser	
290	295	300
His Ser Gly Arg Tyr Met Met Thr Arg	Asp Tyr Leu Ser Val Lys	
305	310	315
Val Trp Asp Leu Asn Met Glu Ser Arg	Pro Val Glu Thr His Gln	
320	325	330
Val His Glu Tyr Leu Arg Ser Lys Leu	Cys Ser Leu Tyr Glu Asn	
335	340	345
Asp Cys Ile Phe Asp Lys Phe Glu Cys	Cys Trp Asn Gly Ser Asp	
350	355	360
Ser Ala Ile Met Thr Gly Ser Tyr Asn	Asn Phe Phe Arg Met Phe	
365	370	375
Asp Arg Asp Thr Arg Arg Asp Val Thr	Leu Glu Ala Ser Arg Glu	
380	385	390
Ser Ser Lys Pro Arg Ala Ser Leu Lys	Pro Arg Lys Val Cys Thr	
395	400	405
Gly Gly Lys Arg Arg Lys Asp Glu Ile	Ser Val Asp Ser Leu Asp	
410	415	420
Phe Asn Lys Lys Ile Leu His Thr Ala	Trp His Pro Val Asp Asn	
425	430	435
Val Ile Ala Val Ala Ala Thr Asn Asn	Leu Tyr Ile Phe Gln Asp	

Lys Ile Asn

440

445

450

<210> 32
<211> 1221
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone Number: 132240

<400> 32
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cagattgccaa agaaaagacc tcacccaaaag gtgtcgagaa ccctgctgta caagagagta 180
accataaaat gttaggtcct cctttggagg tgctgaaaac gttagcctct aaaagaaatg 240
ctgttgcttt tcgaagtttt aacagtcata ttaatgcatc caataactca gaaccatcca 300
gaatgaacat gacttcttta gatgcaatgg atatttcgtg tgcctacagt ggttcatatc 360
ccatggctat aaccctact caaaaaagaa gatcctgtat gccacatcag accccaaatc 420
agatcaagtc gggaaactcca taccgaactc cgaagagtgt gagaagaggg gtggcccccg 480
ttgatgatgg gcgaattcta ggaaccccag actaccttgc acctgagctg ttactaggca 540
gggcccattg tctgcggtta gactggtggg cacttggagt ttgcttgttt gaatttctaa 600
caggaattcc ccttttcaat gatgaaacac cacaacaagt attccagaat attctgaaaa 660
gagatatccc ttggccagaa ggtgaagaaa agttatctga taatgctcaa agtgcagtag 720
aaatactttt aaccattgat gatacaaaag gagctggaat gaaagagcta aaacgtcatc 780
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ttatttaacc tagttcaatg tgcttttaat gtacgttaca gctttcacag agttaaaggg 1080
ctgaaaggaa tatagtcagt aatttatctt aacctcaaaa ctgtatataa atcttcaaag 1140
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tagaggacac taaaaaaaaa a 1221

<210> 33
<211> 542
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone Number: 2180116

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ggagaagtgg atcgacgggc gcctggagga gctgtaccgc ggcagtgagg cagacatgcc 240
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cggcagcctc agccccctcc aggaccgggc cggactgct caccctgac cctcttcac 480
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tt

542

<210> 34

<211> 2778

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 2548, 2557, 2645, 2722, 2557, 2762, 2765

<223> Incyte Clone Number: 2197671

<400> 34

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<210> 35

<211> 1424

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone Number: 2594943

<400> 35

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<212> DNA

<213> Homo sapiens

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<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone Number: 156108

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<212> DNA

<213> Homo sapiens

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<223> Incyte Clone Number: 3173355

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<211> 1260
<212> DNA
<213> Homo sapiens

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<211> 2059
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<223> Incyte Clone Number: 940589

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<211> 1023

<212> DNA

<213> Homo sapiens

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<223> Incyte Clone Number: 304421

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<211> 1182

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone Number: 209854

<400> 48

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 <213> Homo sapiens

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 <221> misc_feature
 <223> Incyte Clone Number: 1384286

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 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte Clone Number: 1512656

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<211> 2145

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone Number: 2098635

<400> 51

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<210> 52

<211> 1454

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone Number: 2446646

<400> 52

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<211> 3225

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone Number: 2764911

<400> 53

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<221> misc_feature

<223> Incyte Clone Number: 3013946

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<223> Incyte Clone Number: 067967

<400> 55

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<211> 1728

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone Number: 346275

<400> 56

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<210> 58

<211> 1290

<212> DNA

<213> Homo sapiens

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<223> Incyte Clone Number: 2696537

<400> 58

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<210> 59

<211> 2281

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone Number: 551178

<400> 59

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2281

<210> 60

<211> 632

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte Clone Number: 619292

<400> 60

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<211> 2347

<212> DNA

<213> Homo sapiens

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<221> misc_feature

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C12N 15/12, C07K 14/47, C12N 9/12, 5/10, C07K 16/18, A61K 38/17		A3	(11) International Publication Number: WO 00/06728
			(43) International Publication Date: 10 February 2000 (10.02.00)
(21) International Application Number: PCT/US99/17132		(72) Inventors; and	
(22) International Filing Date: 28 July 1999 (28.07.99)		(75) Inventors/Applicants (for US only): HILLMAN, Jennifer, L. [US/US]; 230 Monroe Drive #12, Mountain View, CA 94040 (US). LAL, Preeti [IN/US]; 2382 Lass Drive, Santa Clara, CA 95054 (US). TANG, Y., Tom [CN/US]; 4230 Ranwick Court, San Jose, CA 95118 (US). CORLEY, Neil, C. [US/US]; 1240 Dale Avenue #30, Mountain View, CA 94040 (US). GUEGLER, Karl, J. [CH/US]; 1048 Oakland Avenue, Menlo Park, CA 94025 (US). BAUGHN, Mariah, R. [US/US]; 14244 Santiago Road, San Leandro, CA 94577 (US). PATTERSON, Chandra [US/US]; 490 Sherwood Way #1, Menlo Park, CA 94025 (US). BANDMAN, Olga [US/US]; 366 Anna Avenue, Mountain View, CA 94043 (US). AU-YOUNG, Janice [US/US]; 1419 Kains Avenue, Berkeley, CA 94709 (US). GORGONE, Gina, A. [US/US]; 1253 Pinecrest Drive, Boulder Creek, CA 95006 (US). YUE, Henry [US/US]; 826 Lois Avenue, Sunnyvale, CA 94087 (US). AZIMZAI, Yalda [US/US]; 2045 Rock Springs Drive, Hayward, CA 94545 (US). REDDY, Roopa [IN/US]; 1233 W. McKinley Drive, Sunnyvale, CA 94086 (US). LU, Dyung, Aina, M. [US/US]; 55 Park Belmont Place, San Jose, CA 95136 (US). SHIH, Leo, L. [US/US]; Apt. B, 1081 Tanland Drive, Palo Alto, CA 94303 (US).	
(30) Priority Data:			
09/123,494	28 July 1998 (28.07.98)	US	
Not furnished	28 July 1998 (28.07.98)	US	
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Not furnished	14 September 1998 (14.09.98)	US	
09/173,482	14 October 1998 (14.10.98)	US	
Not furnished	14 October 1998 (14.10.98)	US	
60/106,889	3 November 1998 (03.11.98)	US	
60/109,093	19 November 1998 (19.11.98)	US	
60/113,796	22 December 1998 (22.12.98)	US	
09/229,005	12 January 1999 (12.01.99)	US	
Not furnished	12 January 1999 (12.01.99)	US	
(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Applications		(74) Agents: BILLINGS, Lucy, J. et al.; Incyte Pharmaceuticals, Inc., 3174 Porter Drive, Palo Alto, CA 94304 (US).	
US	Not furnished (CIP)		
Filed on	28 July 1998 (28.07.98)		
US	09/123,494 (CIP)		
Filed on	28 July 1998 (28.07.98)		
US	09/152,814 (CIP)		
Filed on	14 September 1998 (14.09.98)		
US	Not furnished (CIP)		
Filed on	14 September 1998 (14.09.98)		
US	09/173,482 (CIP)		
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Filed on	3 November 1998 (03.11.98)		
US	60/109,093 (CIP)		
Filed on	19 November 1998 (19.11.98)		
US	60/113,796 (CIP)		
Filed on	22 December 1998 (22.12.98)		
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(71) Applicant (for all designated States except US): INCYTE PHARMACEUTICALS, INC. [US/US]; 3174 Porter Drive, Palo Alto, CA 94304 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
		Published With international search report.	
		(88) Date of publication of the international search report: 4 May 2000 (04.05.00)	
(54) Title: PHOSPHORYLATION EFFECTORS			
(57) Abstract			
<p>The invention provides human phosphorylation effectors (PHSP) and polynucleotides which identify and encode PHSP. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating, or preventing disorders associated with expression of PHSP.</p>			

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DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/17132

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C12N15/12 C07K14/47 C12N9/12 C12N5/10 C07K16/18 A61K38/17		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07K C12N		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HILLIER, L., ET AL.: "WashU-NCI human EST project" EMBL SEQUENCE DATA LIBRARY, 6 February 1998 (1998-02-06), XP002121148 heidelberg, germany accession no. AA780791 ---	5,6,10, 11
X	ISHIKAWA, K., ET AL.: "prediction of the coding sequences of unidentified human genes. X. The complete sequences of 100 new cDNA clones from brain which can code for large proteins in vitro" DNA RESEARCH, vol. 5, no. 3, 30 June 1998 (1998-06-30), pages 169-176, XP002121149 the whole document --- <div style="text-align: right;">-/--</div>	1-5,9,10
<div style="display: flex; justify-content: space-between;"> <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex. </div>		
* Special categories of cited documents : <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"Z" document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search <div style="text-align: center; font-weight: bold;">9 November 1999</div>		Date of mailing of the international search report <div style="text-align: center; font-weight: bold;">17. 02. 00</div>
Name and mailing address of the ISA European Patent Office, P. B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer <div style="text-align: center; font-weight: bold;">Holtorf, S</div>

INTERNATIONAL SEARCH REPORT

Intern. Patent Application No.

PCT/US 99/17132

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 11234 A (HAWKINS PHILLIP R ; INCYTE PHARMA INC (US); AU YOUNG JANICE (US); G) 19 March 1998 (1998-03-19) the whole document ---	1-19
A	WO 97 02347 A (INCYTE PHARMA INC) 23 January 1997 (1997-01-23) the whole document ---	1-19
A	WALDEN, P.D. AND COWAN, N.J.: "a novel 205-kilodalton testis-specific serine/threonine protein kinase associated with microtubules of the spermatid manchette" MOLECULAR AND CELLULAR BIOLOGY, vol. 13, 1993, pages 7625-7635, XP002121150 the whole document ---	1-19
A	NAGASE, T., ET AL.: "prediction of the coding sequences of unidentified human genes. IX. The complete sequences of 100 new cDNA clones from brain which can code for large proteins in vitro" DNA RESEARCH, vol. 5, 1998, pages 31-39, XP002121152 especially Table 2 + 3 the whole document ---	1-19
A	HILLIER, L., ET AL.: "the WashU-Merck EST project" EMBL SEQUENCE DATA LIBRARY, 25 March 1995 (1995-03-25), XP002121151 heidelberg, germany accession no. t77135 ---	1-19
A	WO 97 48802 A (HAWKINS PHILLIP R ; INCYTE PHARMA INC (US); AU YOUNG JANICE (US); H) 24 December 1997 (1997-12-24) the whole document ---	1-19
P,X	WO 99 04265 A (SAHIN UGUR ; TURECI OZLEM (DE); PFREUNDSCHUH MICHAEL (DE); GOUT IVA) 28 January 1999 (1999-01-28) pages 1-7, 537, 578, 709 claims claims 1-117 -----	1-7, 9-16, 19

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/ 17132

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 19
is directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☒ Claims Nos.: 17, 18, 20
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheets

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-20 partially

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-20 partially

Polynucleotide and polypeptide sequences that show homology to Protein Kinases; especially SEQIDs 1,12 and 32,43; the recombinant expression of the same and uses thereof.

2. Claims: 1-20 partially

Polynucleotide and polypeptide sequences that show homology to PKC-potentiated inhibitory protein of PP1; especially SEQIDs 2 and 33; the recombinant expression of the same and uses thereof.

3. Claims: 1-20 partially

Polynucleotide and polypeptide sequences that show homology to STE20-like Protein Kinases; especially SEQIDs 3 and 34; the recombinant expression of the same and uses thereof.

4. Claims: 1-20 partially

Polynucleotide and polypeptide sequences that show homology to Phosphofructokinases; especially SEQIDs 4 and 35; the recombinant expression of the same and uses thereof.

5. Claims: 1-20 partially

Polynucleotide and polypeptide sequences that show homology to Serin/Threonine Protein Kinases; especially SEQIDs 5,6,10 and 36,37,41; the recombinant expression of the same and uses thereof.

6. Claims: 1-20 partially

Polynucleotide and polypeptide sequences that show homology to Phosphatidylinositol-3-kinases; especially SEQIDs 7 and 38; the recombinant expression of the same and uses thereof.

7. Claims: 1-20 partially

Polynucleotide and polypeptide sequences that show homology to Tyrosine or Tyrosine/serine Protein Kinases; especially SEQIDs 8,13,21 and 39,44,52; the recombinant expression of the same and uses thereof.

8. Claims: 1-20 partially

Polynucleotide and polypeptide sequences that show homology

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

to Calcium /Calmodulin dependent Protein Kinases; especially SEQIDs 9,18,23,25 and 40,49,54,56; the recombinant expression of the same and uses thereof.

9. Claims: 1-20 partially

Polynucleotide and polypeptide sequences that show homology to Tyrosine Phosphatases or Dual specificity phosphatases; especially SEQIDs 11,29,30 and 42,60,61; the recombinant expression of the same and uses thereof.

10. Claims: 1-20 partially

Polynucleotide and polypeptide sequences that show homology to PEST phosphatase interacting protein; especially SEQIDs 14 and 45; the recombinant expression of the same and uses thereof.

11. Claims: 1-20 partially

Polynucleotide and polypeptide sequences that show homology to SH3-binding proteins; especially SEQIDs 15 and 46; the recombinant expression of the same and uses thereof.

12. Claims: 1-20 partially

Polynucleotide and polypeptide sequences that show homology to NIK-kinases; especially SEQIDs 16 and 47; the recombinant expression of the same and uses thereof.

13. Claims: 1-20 partially

Polynucleotide and polypeptide sequences that show homology to Interferon-induced PK regulators; especially SEQIDs 17 and 48; the recombinant expression of the same and uses thereof.

14. Claims: 1-20 partially

Polynucleotide and polypeptide sequences that show homology to Choline-kinases; especially SEQIDs 19 and 50; the recombinant expression of the same and uses thereof.

15. Claims: 1-20 partially

Polynucleotide and polypeptide sequences that show homology to MAP-related Protein kinases; especially SEQIDs 20 and 51; the recombinant expression of the same and uses thereof.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

16. Claims: 1-20 partially

Polynucleotide and polypeptide sequences that show homology to Ribosomal S6 Protein kinases; especially SEQIDs 22 and 53; the recombinant expression of the same and uses thereof.

17. Claims: 1-20 partially

Polynucleotide and polypeptide sequences that show homology to Protein kinases Dyrk2; especially SEQIDs 24 and 55; the recombinant expression of the same and uses thereof.

18. Claims: 1-20 partially

Polynucleotide and polypeptide sequences that show homology to Protein Phosphatases 2A; especially SEQIDs 26,28,31 and 57,59,62; the recombinant expression of the same and uses thereof.

19. Claims: 1-20 partially

Polynucleotide and polypeptide sequences that show homology to MAP-kinase Phosphatases; especially SEQIDs 27 and 58; the recombinant expression of the same and uses thereof.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 17,18,20

Claims 17,18 and in part 20 refer to an antagonist and agonist of the polypeptides without giving a true technical characterization. Moreover, no such compounds are defined in the application. In consequence, the scope of said claims is ambiguous and vague, and their subject-matter is not sufficiently disclosed and supported (Art. 5 and 6 PCT). No search can be carried out for such purely speculative claims whose wording is, in fact, a mere recitation of the results to be achieved.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/17132

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9811234 A	19-03-1998	US 5773699 A	30-06-1998
		US 5863780 A	26-01-1999
		AU 4261197 A	02-04-1998
		EP 0927257 A	07-07-1999
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		EP 0781336 A	02-07-1997
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		EP 0910639 A	28-04-1999
		US 5922844 A	13-07-1999
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CORRECTED VERSION

(19) World Intellectual Property Organization
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(43) International Publication Date
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C07K 14/47, C12N 9/12, 5/10, C07K 16/18, A61K 38/17

(21) International Application Number: PCT/US99/17132

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60/155,196	14 September 1998 (14.09.1998)	US
60/155,239	14 October 1998 (14.10.1998)	US
60/106,889	3 November 1998 (03.11.1998)	US
60/109,093	19 November 1998 (19.11.1998)	US
60/113,796	22 December 1998 (22.12.1998)	US
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US	60/155,213 (CIP)
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US	60/155,196 (CIP)
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(54) Title: PHOSPHORYLATION EFFECTORS

(57) Abstract: The invention provides human phosphorylation effectors (PHSP) and polynucleotides which identify and encode PHSP. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating, or preventing disorders associated with expression of PHSP.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.